

東京医学

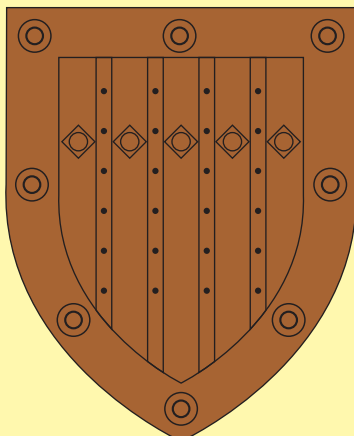
THE TOKYO JOURNAL OF MEDICAL SCIENCES

October 2024

Vol.149

ANNUAL REPORT OF
THE GRADUATE SCHOOL OF MEDICINE
AND
THE FACULTY OF MEDICINE
THE UNIVERSITY OF TOKYO

REPORTS FOR THE PERIOD April 2023 — March 2024



共同編集 東京大学医師会・東京大学医学部

JOINTLY EDITED BY
THE UNIVERSITY OF TOKYO MEDICAL SOCIETY
THE UNIVERSITY OF TOKYO FACULTY OF MEDICINE

学術刊行物

東京医学

Tokyo J. Med. Sci.

ANNUAL REPORT OF THE GRADUATE SCHOOL OF
MEDICINE

THE FACULTY OF MEDICINE

THE UNIVERSITY OF TOKYO

REPORTS FOR THE PERIOD April 2023-March 2024

Introduction

This is volume 149 (the edition of year 2024) of the annual report by the University of Tokyo's Graduate School of Medicine and Faculty of Medicine.

In it are recorded the past year's research, educational, clinical, and other activities of the Graduate School of Medicine and Faculty of Medicine.

It reports our accomplishments, and each year we make such a document freely available by publishing it on compact disk and on the Internet, expecting it to be used for internal and external evaluations.

The University of Tokyo's Faculty of Medicine was founded 160 years ago. Since then we have consistently driven Japan's progress in medical research, medical education, and clinical care, and in some fields we have become world leaders.

We have more than 1000 students in the Graduate School of Medicine, and with as many as 150 foreign researchers and students we are an international center for medical research and education.

Pursuing excellence in our research, educational, and clinical activities, we will continue meeting the needs for tomorrow's pioneers in medical sciences and clinical care.

Masaomi Nangaku, Dean
Graduate School of Medicine and Faculty of Medicine
The University of Tokyo

October, 2024

CONTENTS

Introduction

History

Organization Chart

Teaching, Research, Secretarial and Administrative Staffs

The University of Tokyo, Graduate School of Medicine

Molecular Cell Biology

1. Cell Biology and Anatomy	1
Department of Cell Biology	2
Department of Structural Biology	4
Department of Cytoarchitectonics	6
Department of Cellular Neurobiology	8
2. Biochemistry and Molecular Biology	11
Department of Molecular Biology	12
Department of Genome Informatics	16
Department of Physiological Chemistry and Metabolism	19
3. Advanced Structural Studies	23
Department of Advanced Structural Studies	24

Functional Biology

1. Physiology	26
Department of Integrative Physiology	27
Department of Cellular and Molecular Physiology	30
Department of Neurophysiology	34
2. Pharmacology	36
Department of Cellular and Molecular Pharmacology	37
Department of Systems Pharmacology	39

Pathology, Immunology and Microbiology

1. Pathology	43
Department of Pathology and Diagnostic Pathology	44
Department of Molecular Pathology	48

2. Microbiology	50
Department of Microbiology	51
Department of Infection Control and Prevention	54
3. Immunology	58
Department of Immunology	59
Radiology and Biomedical Engineering	
1. Radiology	64
Department of Radiology	65
2. Biomedical Engineering	68
Department of System Physiology	69
Department of Chemical Biology and Molecular Imaging	74
Division of Integrative Genomics	77
Neuroscience	
1. Basic Neuroscience	81
Department of Neuropathology	82
Department of Neurochemistry	86
2. Integrative Medical Neuroscience	92
Department of Child Neuropsychiatry	93
3. Clinical Neuroscience	96
Department of Neuropsychiatry	97
Department of Neurology	100
Department of Neurosurgery	106
Social Medicine	
1. Occupational, Environmental and Preventive Medicine	114
Department of Molecular Preventive Medicine	115
Department of Public Health / Department of Health Policy	119
2. Forensic Medicine, and Medical Informatics and Economics	124
Department of Forensic Medicine	125
Department of Biomedical Informatics	129

Internal Medicine

1. Medicine I	132
Department of Cardiovascular Medicine	133
Department of Respiratory Medicine	137
Department of Gastroenterology	143
2. Medicine II	148
Department of Nephrology and Endocrinology	149
Department of Diabetes and Metabolic Diseases	154
Department of Hematology and Oncology	162
Department of Allergy and Rheumatology	166
Department of Infectious Diseases (Internal Medicine)	170
Department of Stress Science and Psychosomatic Medicine	174
3. Clinical Laboratory Medicine and Pathology	177
Department of Clinical Laboratory Medicine (See Department of Clinical Laboratory [P.486])	
Department of Transfusion Medicine	178

Reproductive, Developmental and Aging Sciences

1. Obstetrics and Gynecology	181
Department of Reproductive Endocrinology	182
Department of Gynecologic Oncology	185
Department of Perinatal Medicine	187
Department of Molecular and Cellular Reproductive Medicine	189
2. Pediatric Sciences	192
Department of Pediatrics, Department of Developmental Pediatrics	193
Department of Pediatric Surgery	198
3. Aging Sciences	202
Department of Geriatric Medicine, Department of Aging Research	203

Surgical Sciences

1. Surgery	210
Department of Thoracic Surgery	211
Department of Cardiac Surgery	215
Department of Gastrointestinal Surgery	220
Hepato-biliary-Pancreatic Surgery Division and Artificial Organ and Transplantation Division	224
Department of Urology	227

Department of Surgical Oncology	234
Department of Vascular Surgery	238
Department of Brest and Endocrine Surgery	241
2. Sensory and Motor System Medicine	244
Department of Dermatology	245
Department of Plastic and Reconstructive Surgery	248
Department of Oral-Maxillofacial Surgery	251
Department of Orthopaedic Surgery	255
Department of Ophthalmology	264
Department of Otolaryngology and Head and Neck Surgery	268
Department of Rehabilitation Medicine	276
3. Vital Care Medicine	279
Department of Anesthesiology	280
Department of Emergency and Critical Care Medicine	284
Health Sciences and Nursing	
1. Health Sciences	287
Department of Health Sociology	
(See Departments of Health and Social Behavior & Health Education and Health Sociology [P.367])	
Department of Mental Health	288
Department of Biostatistics / Epidemiology and Preventive Health Sciences	292
Department of Social Gerontology	
(See Departments of Health and Social Behavior & Health Education and Health Sociology [P.367])	
Department of Biomedical Ethics & Department of Health Promotion Sciences	295
2. Preventive and Administrative Nursing	298
Department of Nursing Administration / Advanced Clinical Nursing	299
Department of Family Nursing	302
Department of Community Health Nursing / Public Health Nursing	305
3. Clinical Nursing	307
Department of Gerontological Home Care and Long-term Care Nursing/Palliative Care Nursing	308
Department of Midwifery and Women's Health	312
Department of Psychiatric Nursing	316
Department of Gerontological Nursing / Wound Care Management	321

International Health

1. International Social Medicine	327
Department of Global Health Policy	328
Department of Community and Global Health	332
2. International Biomedical Sciences	335
Department of Human Genetics	336
Department of Developmental Medical Sciences	338
Department of Human Ecology	341
Department of Biomedical Chemistry	345

School of Public Health

1. Epidemiology and Health Sciences	348
Department of Biostatistics	
(See Department of Biostatistics / Epidemiology and Preventive Health Sciences [P.292])	
Department of Social and Preventive Epidemiology	349
Department of Clinical Epidemiology and Health Economics	352
Department of Health Communication	363
2. Behavioral Health Sciences	366
Department of Mental Health (See Department of Mental Health [P.288])	
Department of Health Sociology and Health Education	
(See Departments of Health and Social Behavior & Health Education and Health Sociology [P.367])	
Departments of Health and Social Behavior & Health Education and Health Sociology	367
Department of Biomedical Ethics & Department of Health Promotion Sciences	
(See Department of Biomedical Ethics & Department of Health Promotion Sciences [P.295])	
3. Health Services Sciences	371
Department of Health Policy	
(See Department of Public Health / Department of Health Policy [P.119])	
Department of Healthcare Informatics (See Department of Biomedical Informatics [P.129])	
Department of Clinical Information Engineering	372
Department of Forensic Medicine and Medical Law	
(See Department of Forensic Medicine [P.125])	
Department of Global Environmental Health	374

Endowed Department	377
Department of Artificial Intelligence in Healthcare	378
Science for joint reconstruction (See Department of Orthopaedic Surgery [P.255])	

Department of Bone & Cartilage Regenerative Medicine (See Central Clinical Facilities Division of Tissue Engineering [P.548])	
Department of Osteoimmunology	381
Department of Computational Diagnostic Radiology and Preventive Medicine	385
Department of Home Care Medicine	388
Department of Therapeutic Strategy for Heart Failure	390
Department of Biostatistics and Bioinformatics	394
Department of Advanced Cardiology	397
Department of Advanced Clinical Science and Therapeutics	402
Comprehensive Radiation Oncology	404
Department of Immunotherapeutics	407
Social Cooperation Program	410
Department of Eat-loss Medicine (See Central Clinical Facilities Division of Tissue Engineering [P.548])	
Department of Medical Information Engineering	411
Health Economy and Society Policy	413
Department of Healthcare Quality Assessment	416
Laboratory for Cryo-Electron Microscopy	419
Department of Cellular and Tissue Communication	421
Department of Next-generation Endoscopic Computer Vision	424
Next-Generation Precision Medicine Development Laboratory	426
Department of Tissue Stem Cells and Life Dentistry	429
Department of Digital Mental Health	431
Department of Prevention of Diabetes and Lifestyle-Related Diseases	434
Department of Pain & Palliative Medical Sciences	437
Department of Nutritional Epidemiology and Behavioural Nutrition	440
Department of Precision Medicine Neurology	442
Department of Health Services Research	445
Division of Chronic Kidney Disease (CKD) Pathophysiology	451
Department of Functional Genomics and Immunological Diseases (See Department of Allergy and Rheumatology [P.166])	
Department of Retinal Biology and Pathology	454
Department of Real-world Evidence	457
Department of Lipidomics	461
Clinical stem cell biology (See Central Clinical Facilities Division of Tissue Engineering [P.548])	
Department of Preventive Medicine for Locomotive Organ Disorders	464

University Hospital

Clinical Services	467

Internal Medicine

Cardiovascular Medicine (See Department of Cardiovascular Medicine [P.133])

Respiratory Medicine (See Department of Respiratory Medicine [P.137])

Gastroenterology (See Department of Gastroenterology [P.143])

Nephrology and Endocrinology (See Department of Nephrology and Endocrinology [P.149])

Diabetes and Metabolic Diseases (See Department of Diabetes and Metabolic Diseases [P.154])

Hematology and Oncology (See Department of Hematology and Oncology [P.162])

Allergy and Rheumatology (See Department of Allergy and Rheumatology [P.166])

Infectious Diseases (See Department of Infectious Diseases (Internal Medicine) [P.170])

Neurology (See Department of Neurology [P.100])

Geriatric Medicine

(See Department of Geriatric Medicine, Department of Aging Research [P.203])

Psychosomatic Medicine

(See Department of Stress Science and Psychosomatic Medicine [P.174])

Surgery

Stomach and Esophageal Surgery (See Department of Gastrointestinal Surgery [P.220])

Colon and Rectal Surgery (See Department of Surgical Oncology [P.234])

Hepatobiliary Pancreatic Surgery

(See Hepato-biliary-Pancreatic Surgery Division and Artificial Organ and Transplantation Division [P.224])

Vascular Surgery (See Department of Vascular Surgery [P.238])

Breast and Endocrine Surgery

(See Department of Metabolic Care and Endocrine Surgery [P.241])

Artificial Organ and Transplantation Surgery

(See Hepato-biliary-Pancreatic Surgery Division and Artificial Organ and Transplantation Division [P.224])

Cardiovascular Surgery (See Department of Cardiac Surgery [P.215])

Thoracic Surgery (See Department of Thoracic Surgery [P.211])

Neurosurgery (See Department of Neurosurgery [P.106])

Anesthesiology and Pain Relief Center (See Department of Anesthesiology [P.280])

Urology and Andrology (See Department of Urology [P.227])

Gynecologic Surgery (See Obstetrics and Gynecology [P.181])

Sensory and Motor System Medicine

Dermatology (See Department of Dermatology [P.245])

Ophthalmology (See Department of Ophthalmology [P.264])

Orthopaedic Surgery and Spinal Surgery (See Department of Orthopaedic Surgery [P.255])

Otorhinolaryngology and Head and Neck Surgery	
(See Department of Otorhinolaryngology and Head & Neck Surgery [P.268])	
Rehabilitation Medicine (See Department of Rehabilitation Medicine [P.276])	
Plastic, Reconstructive and Aesthetic Surgery	
(See Department of Plastic and Reconstructive Surgery [P.248])	
Oral-Maxillofacial Surgery and Orthodontics	
(See Department of Oral-Maxillofacial Surgery [P.251])	
Pediatrics, Perinatal and Women's Medicine	
Pediatrics	
(See Department of Pediatrics, Department of Developmental Pediatrics [P.193])	
Pediatrics Surgery (See Department of Pediatric Surgery [P.198])	
Obstetrics and Gynecology	
(See Department of Reproductive Endocrinology / Department of Gynecologic Oncology /	
Department of Perinatal Medicine [P.177/P.180/P.182])	
Neuropsychiatry	
Neuropsychiatry (See Department of Neuropsychiatry [P.97])	
Radiology	
Radiology (See Department of Radiology [P.65])	
Emergency and Critical Care Medicine	
Emergency and Critical Care Medicine	
(See Department of Emergency and Critical Care Medicine [P.284])	
Cross-Sectional Services	
Advanced Medical Center for Heart Failure	468
Department of Clinical Genomics	471
Department of Child Psychiatry	473
Children, AYA and Family Centered Mental Care Center	
(See Department of Child Psychiatry [P.473])	
Department of Pain and Palliative Medicine	477
Central Clinical Services	481
Department of Pharmacy	482
Department of Clinical Laboratory	486
Department of Blood Transfusion	
(See Department of Transfusion Medicine [P.178])	
Department of Pathology	491
Department of Infection Control and Prevention	
(See Department of Infection Control and Prevention [P.54])	
Radiology Center	495
Rehabilitation Center	498

Surgical Center	501
Central Supply Service	504
Department of Endoscopy and Endoscopic Surgery	506
Department of Hemodialysis and Apheresis	510
Department of Intensive Care Unit (See Department of Emergency and Critical Care Medicine [P.284])	
Immune-Mediated Diseases Therapy Center	513
Tissue Bank.....	515
Department of Corneal Transplantation	517
Department of Cell Therapy and Transplantation Medicine	520
Clinical Nutrition Center	523
Swallowing Center	529
International Medical Center	532
Center for Epidemiology and Preventive Medicine	533
Palliative Care Consultation Team (See Department of Pain and Palliative Medicine [P.477])	
Medical Community Network and Discharge Supporting Center	536
Cancer Resource Center	538
 Clinical Research Services	
Clinical Research Promotion Center	540
Division of Tissue Engineering	548
Cooperative Unit of Medicine and Engineering Research	552
Genomic Research Support Center	557
BioResource Center	560
 Hospital Management Services	
Department of Clinical Research Governance	562
Department of Healthcare Information Management	564
University Hospital Medical Information Network Center	566
Department of Disaster Medical Management	568
 Center for Disease Biology and Integrative Medicine	570
Laboratory of Molecular Biomedicine for Pathogenesis	571
Laboratory of Structural Physiology	573
Laboratory of Biomedical Equipment and Biomaterials	575
Laboratory of Clinical Biotechnology	577
Laboratory of Microenvironmental and Metabolic Health Sciences	583
Laboratory of Animal Resources	588
Laboratory of Molecular Radiology	591
Laboratory of Biomedical Informatics.....	593

The International Research Center for Medical Education (IRCME)	596
Department of Medical Education Studies	597
Department of International Cooperation for Medical Education	599
Global Nursing Research Center	601
Center for Diversity in Medical Education and Research	605
Office of International Academic Affairs	607
MD Scientist Training Program	609
Museum of Health and Medicine	612
Office for Human Research Studies (OHRS)	614
Life Sciences Core Facility (LSCF)	616
The Office for Clinical Practice and Medical Education	618
Advisory Office for Conflict of Interest	620

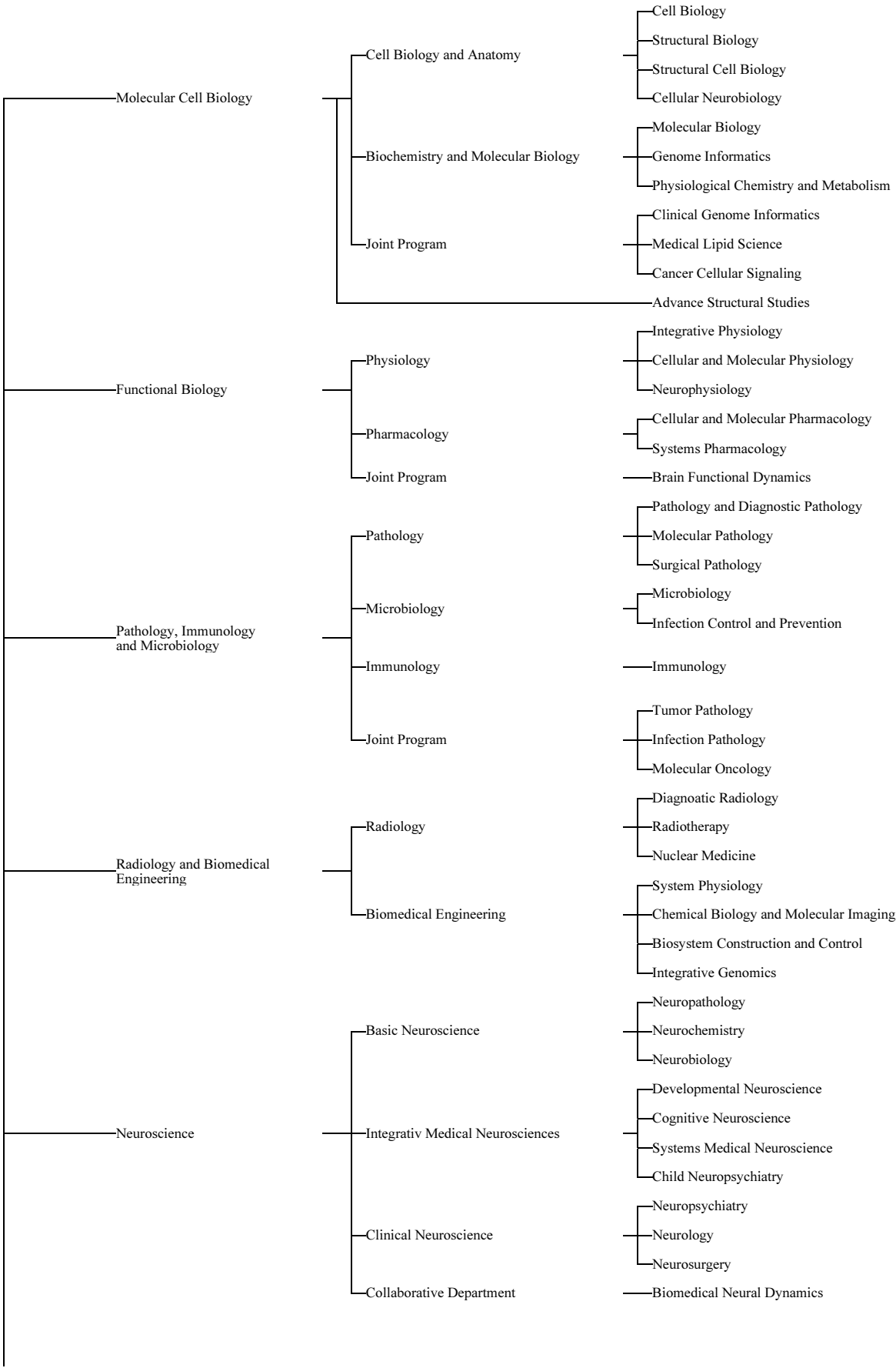
History

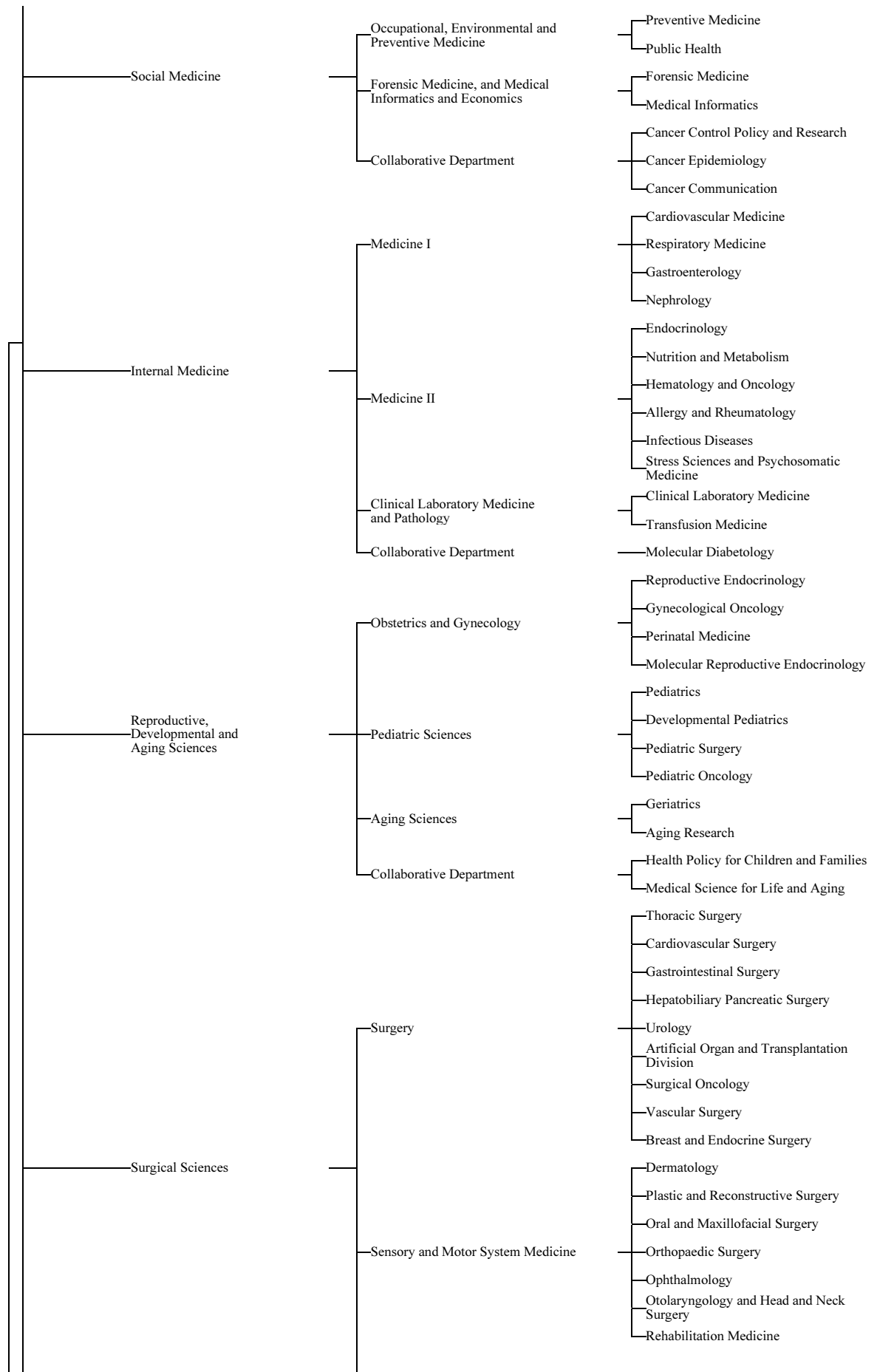
1858	May	Practitioners, trained in Dutch (European) medicine in Edo (Tokyo), laid out money to establish the Shutojo (vaccination center) in Kanda Mitamagaie.
	Nov.	Shutojo was destroyed in a fire that had spread from Kanda Aioicho. Shutojo continued its operations at other sites such as the residence of Ito Genboku.
1859	Sep.	Shutojo was reconstructed at Shitaya Izumibashi Dohri.
1860	Oct.	Shutojo became an official medical institution of the Shogunate Government.
1861	Oct.	Shutojo was renamed as Seiyo Igaku-Sho (Institute of Western Medicine) and offered courses of Western Medicine in the fields of Education, Autopsy, and Vaccination.
1863	Feb.	Seiyo Igaku-Sho was renamed as Igaku-Sho (Institute of Medicine).
1868	Jul.	Igaku-Sho, affiliated with the Military Hospital which had been moved from Yokohama to Todo residence in Shitaya, was renamed as Daibyoin (the Great Hospital).
1869	Feb.	The Daibyoin was renamed as Igakko-Ken-Byoin (Medical School and Hospital).
	Dec.	Igakko-Ken-Byoin was renamed as Daigaku Toko (University East Building).
1871	Jul.	The Ministry of Education was established and Daigaku-Toko was renamed as Toko (East Building).
1872	Aug.	A School System was established. Toko was renamed as Daiichi-Daigaku-Ku- Igakko (The First University District Medical School).
1874	May	Daiichi-Daigaku-Ku-Igakko was renamed as Tokyo-Igakko (Tokyo Medical School).
1876	Nov.	Tokyo-Igakko was moved to Hongo.
1877	Apr.	Tokyo Igakko, affiliated with Tokyo-Kaisei School, was renamed as The University of Tokyo. Tokyo Medical School was renamed as The University of Tokyo Faculty of Medicine.
1886	Mar.	The University of Tokyo was renamed as Imperial University, and The University of Tokyo Faculty of Medicine was renamed as the Imperial University Medical College. A Graduate School was established.
1897	Jun.	The Imperial University was renamed as Tokyo Imperial University.
1917	Aug.	Eiraku Hospital, affiliated with the Ministry of Education Medical Practice License Examination, moved to Tokyo Imperial University and was renamed as Koishikawa Hospital affiliated with Tokyo Imperial University Medical College.
1919	Apr.	A faculty system was established renaming Tokyo Imperial University Medical College as the Faculty of Medicine.
1931	Feb.	The first building of the Faculty of Medicine was constructed.
1936	Jan.	The Brain Research Laboratory was built with funds donated by Mr. Hisasaburo Horikoshi.
	Nov.	The second building of the Faculty of Medicine (main building) was constructed.
1947	Sep.	Tokyo Imperial University was renamed as The University of Tokyo.
1950	Apr.	The Institute of Nursing was renamed as The University Nursing School.
1953	Apr.	The School of Health Care and Nursing was founded.

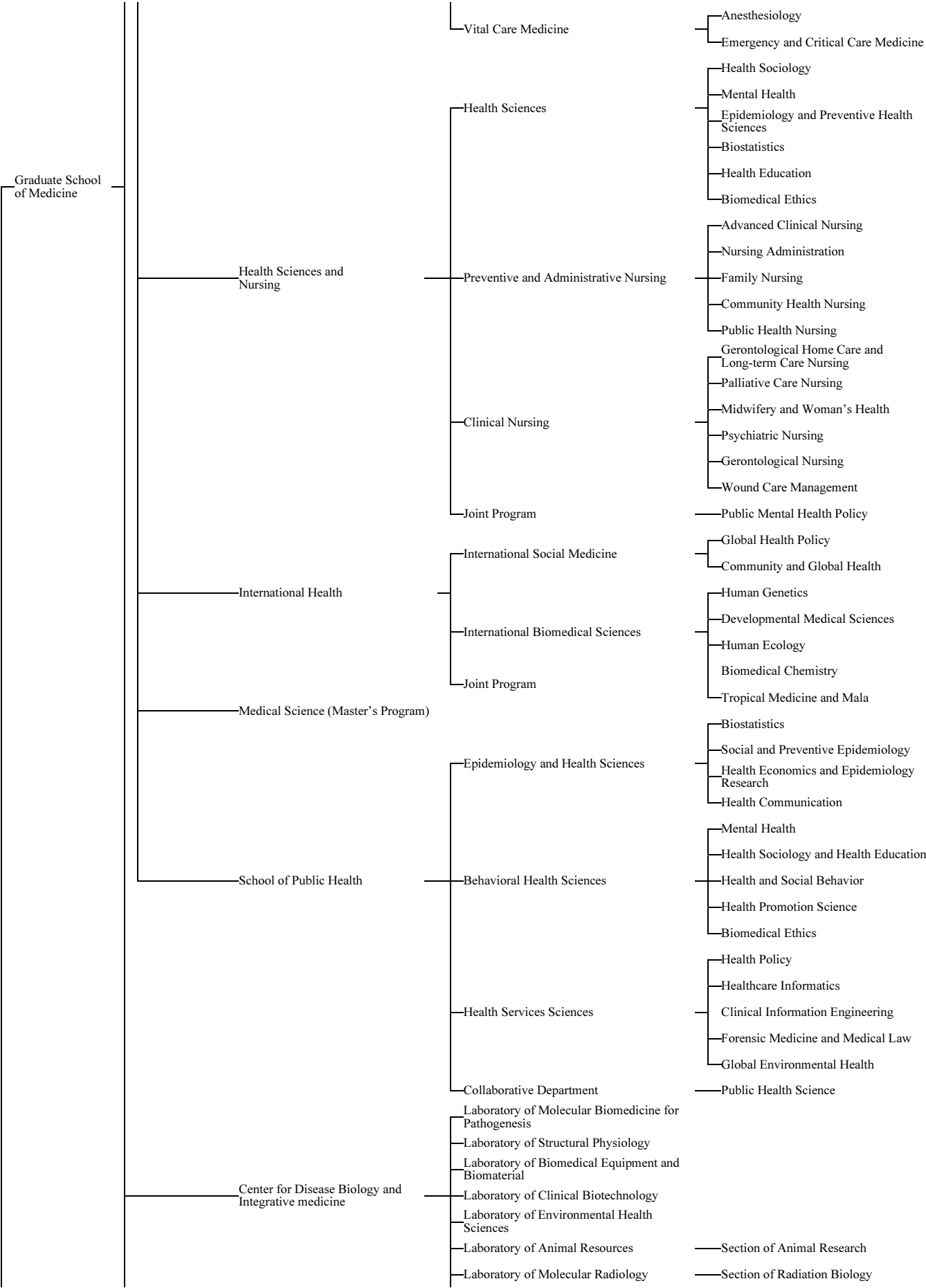
- Jul. The Graduate School was founded, and the Division of Medical Doctor Biological Science was established. The Brain Research Laboratory became the Brain Research Institute of the Faculty of Medicine.
- 1956 Apr. The Midwives School was established.
- 1958 Apr. The Division of Pharmaceutical Sciences became an independent faculty.
May The University of Tokyo Faculty of Medicine celebrated its centennial anniversary.
- 1961 Nov. The Medical Library was built in commemoration of the centenary.
- 1962 Apr. The Institute of Medical Electronics was established.
- 1965 Apr. The Research Institute of Logopedics and Pediatrics was established. The School of Health Care and Nursing was reorganized as the School of Health Sciences. The Graduate School of The University of Tokyo was reorganized and the Division of Medical Doctor Biological Science became the Faculty of Medicine. The Health science Course was established in the Medical Science Division.
- 1966 Sep. The third building of the Faculty of Medicine was constructed.
- 1971 Apr. The Laboratory of Animal Experiments was established.
- 1973 Mar. The Animal Center for Biomedical Research was constructed.
- 1983 Jan. An annex of the third building of the Faculty of Medicine was constructed.
- 1985 Oct. The office of International Academic Affairs was established.
- 1987 Apr. Specialized courses were introduced to the Graduate School of Medicine.
- 1992 Apr. The School of Health Sciences became the School of Health Science and Nursing. The School of International Health was established in the Medical Science Division.
Jul. The Radiation Research Institute was established.
- 1995 Apr. As a result of the shift to the chair system of the Graduate School of Medicine, four divisions, Third Basic Medicine, Social Medicine, Third and Fourth Clinical Medicine, were replaced with Pathology, Immunology and Microbiology, Social Medicine, Reproduction and Development, and Aging Science and Surgery.
- 1996 Apr. As a result of the shift to the chair system of the Graduate School of Medicine, three divisions, First Clinical Medicine, Health Science, and International Health, were replaced with Internal Medicine, Health Science and Nursing, and International Health.
- 1997 Apr. As a result of the shift to the chair system of the Graduate School of Medicine, three divisions, First and Second Basic Medicine, and Second Clinical Medicine, were replaced with Molecular Cell Biology, Functional Biology, Radiology and Biomedical Engineering, and Neuroscience.
As a result of the above-mentioned reorganization, three institutes, the Institute of Brain Research, the Institute of Medical Electronics, and the Institute of Logopedics and Phoniatrics were made redundant.
- 1999 Apr. The Medical Science master's program was established in the Graduate School of Medicine. This course accepts graduates of all faculties except those from Schools of Medicine, Dentistry, and Veterinary Medicine.

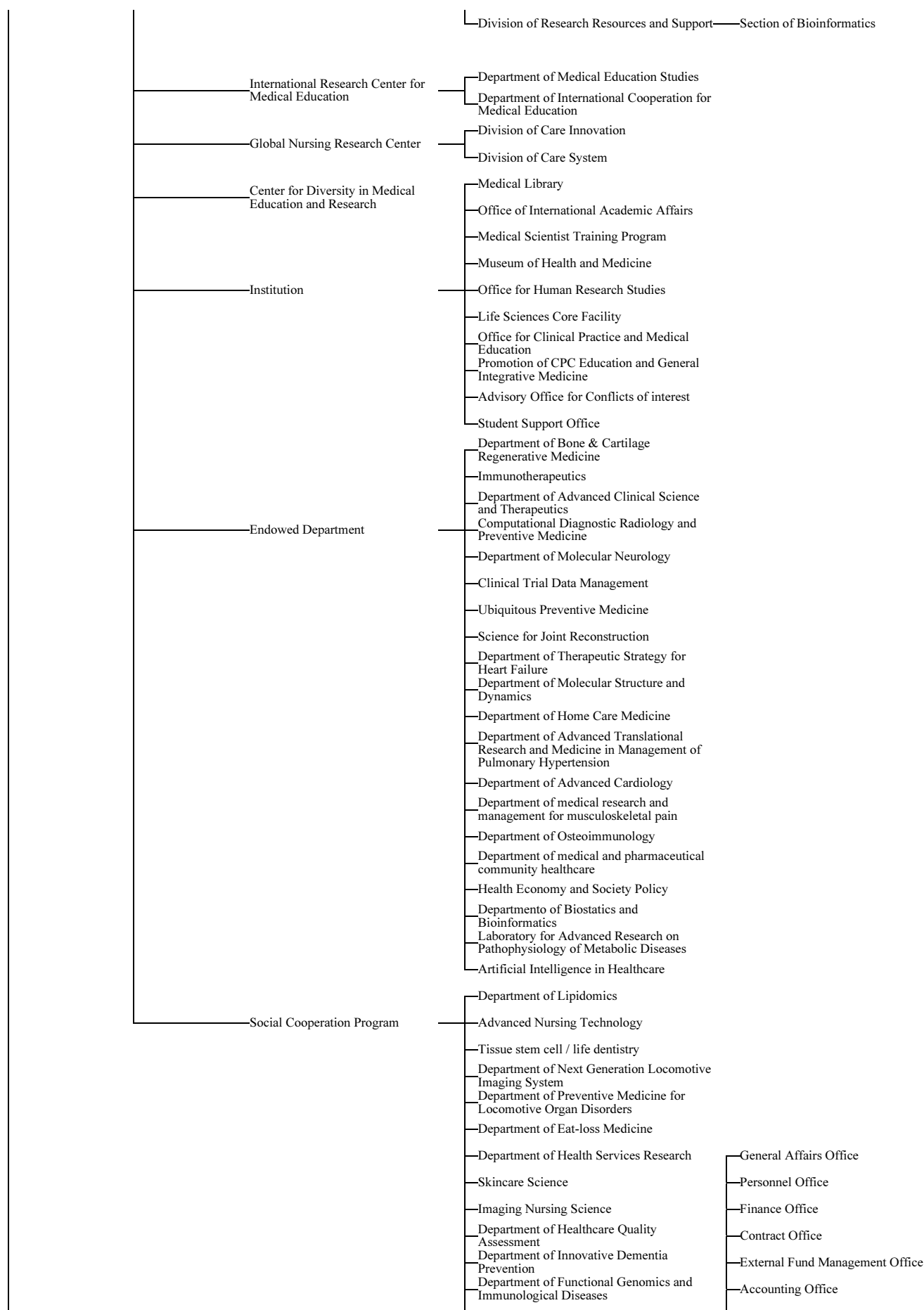
2000	Apr.	The International Research Center for Medical Education was established (A shared facility for education and research).
2001	Apr.	The University Branch Hospital was united with the University Hospital.
	Dec.	Experimental Building (First Stage) was constructed.
2002	Mar.	Nursing School and Midwives School was Closed.
2003	Apr.	The Center for Disease Biology and Integrative Medicine was established.
		The Radiation Research Institute and the Laboratory of Animal Experiments were integrated into the Center for Disease Biology and Integrative Medicine.
2004	Apr.	All the National Universities owned by the Japanese Government became National University Corporations and the University of Corporation.
2005	Mar.	Experimental Building (Second Stage) was constructed.
2007	Apr.	The School of Public Health was established. This school offers programs for Master of Public Health.
2008	May	The University of Tokyo Faculty of Medicine and the University of Tokyo Hospital celebrated their 150th anniversary.
2010	Apr.	The School of Health Science and Nursing became the School of Integrated Health Sciences.
2011	Jan.	The Museum of Health and Medicine was established.
2012	Apr.	The Office for research Ethics Support was established.
2013	Apr.	The International Research Center for Medical Education became a facility of the Graduate School of medicine.
	Oct.	The Life Sciences Core facility was established.
2015	Apr.	The Office for Clinical Practice and Medical Education was established.
2016	Apr.	The Advisory office for Conflicts of interest was established.
2017	Apr.	The Global Nursing Research Center was established.
	Apr.	The Institute for Life Science Research and Education was established.
2019	May	The Bioethics Collaborative Research Organization was established.
2020	Apr.	The Collaborative Research Organization for Structural Life Sciences was established.
2021	Apr.	UTokyo Center for Diversity in Medical Education and Research was established.

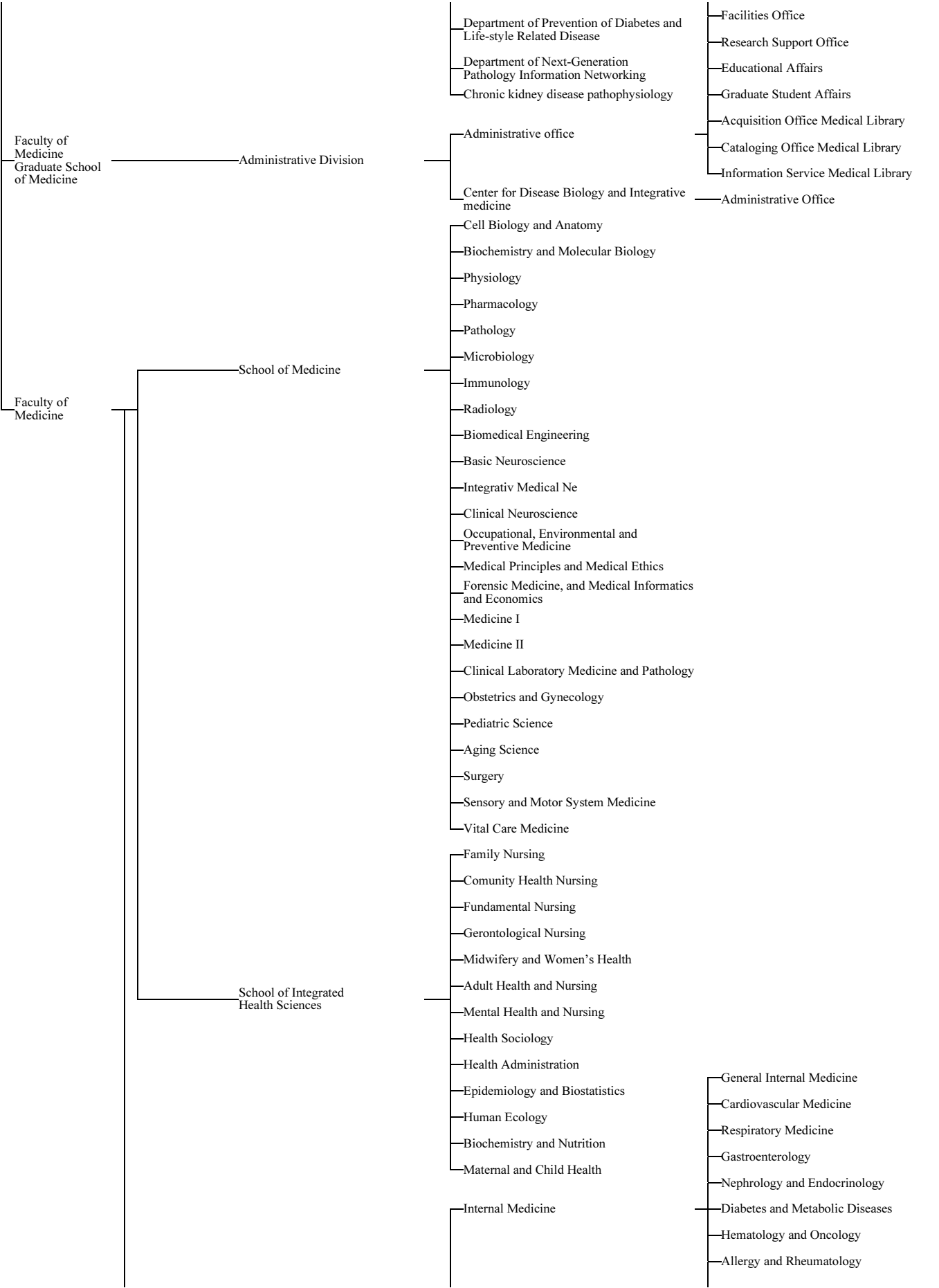
Organization Chart

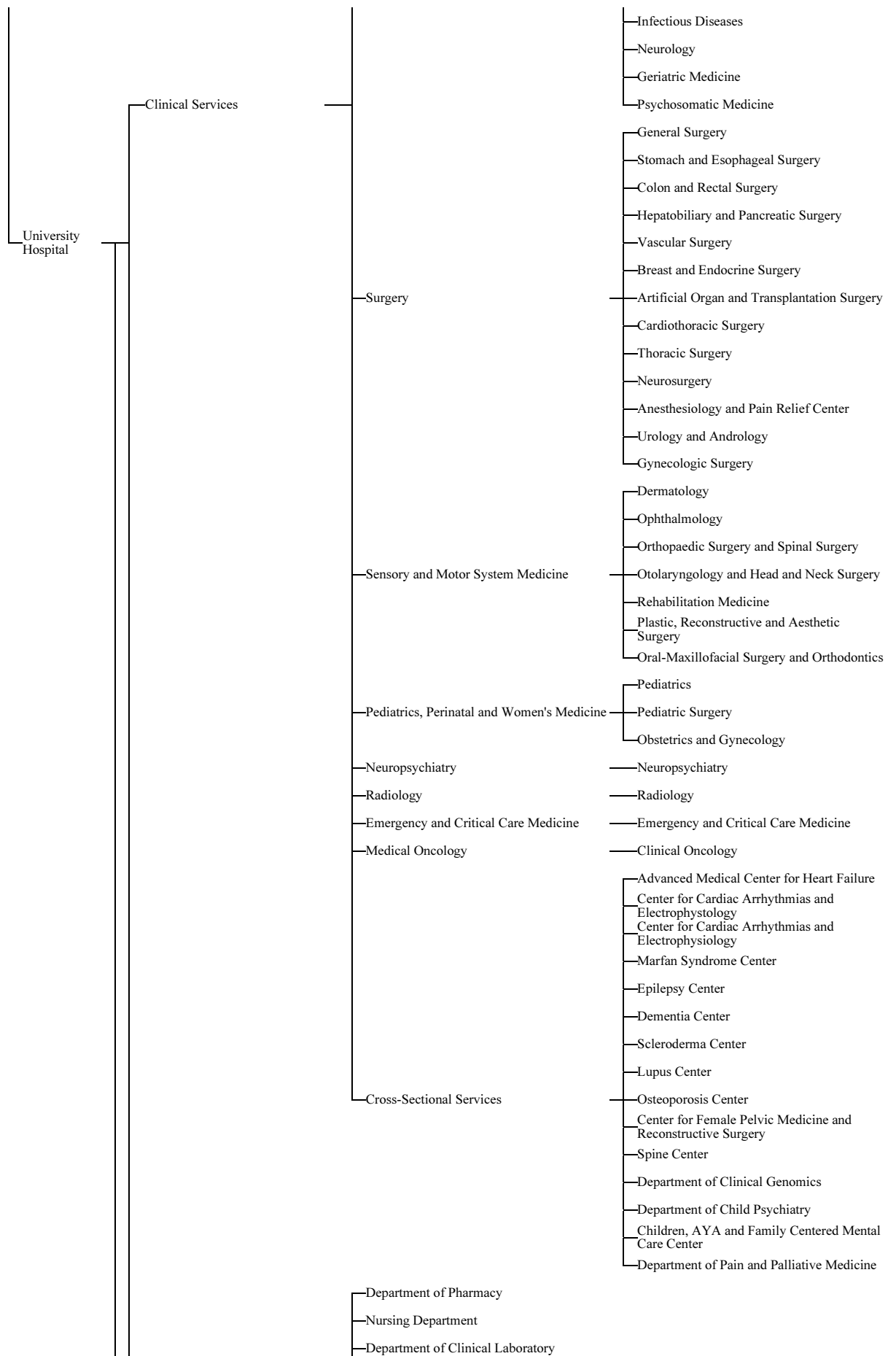


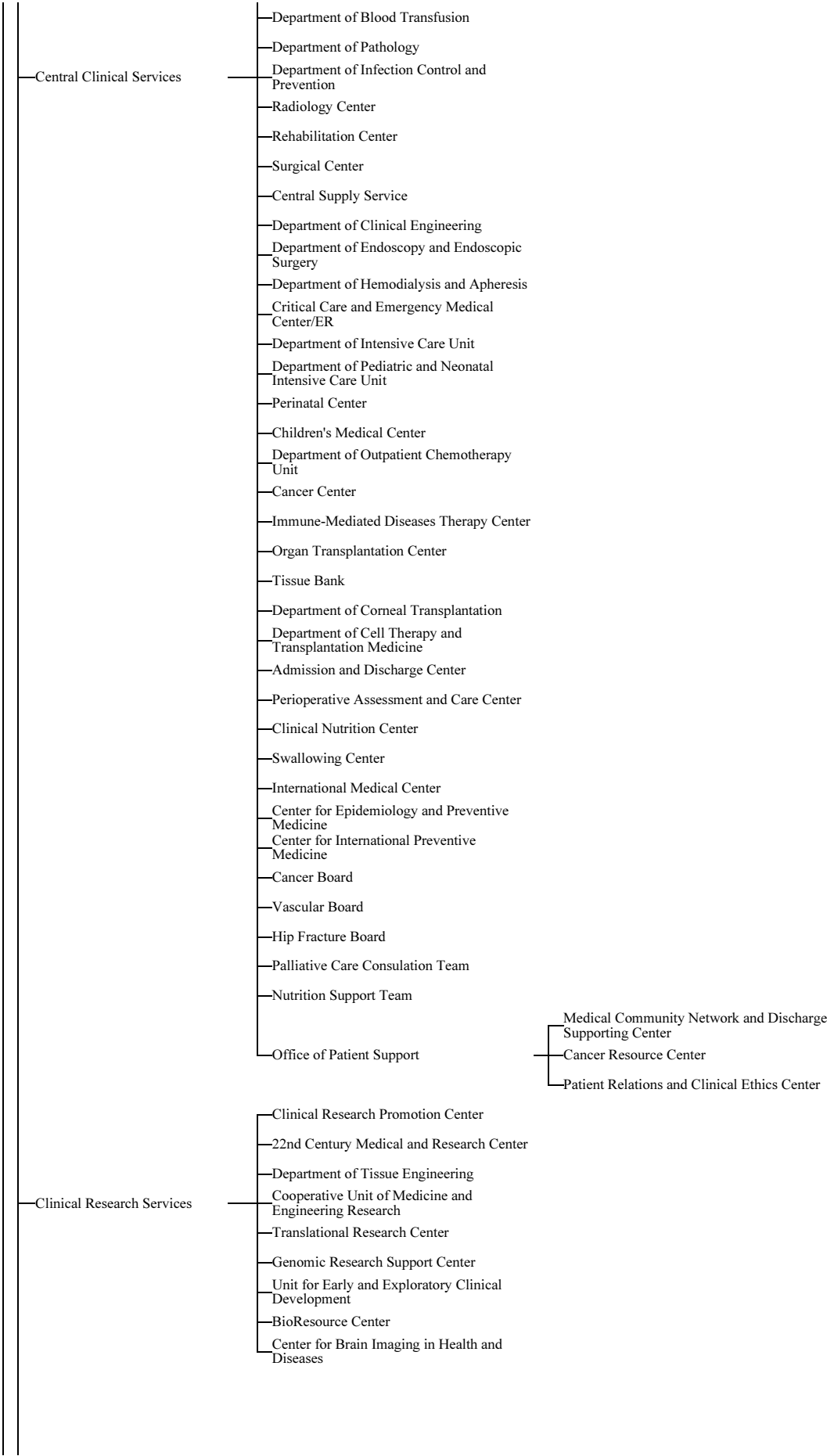


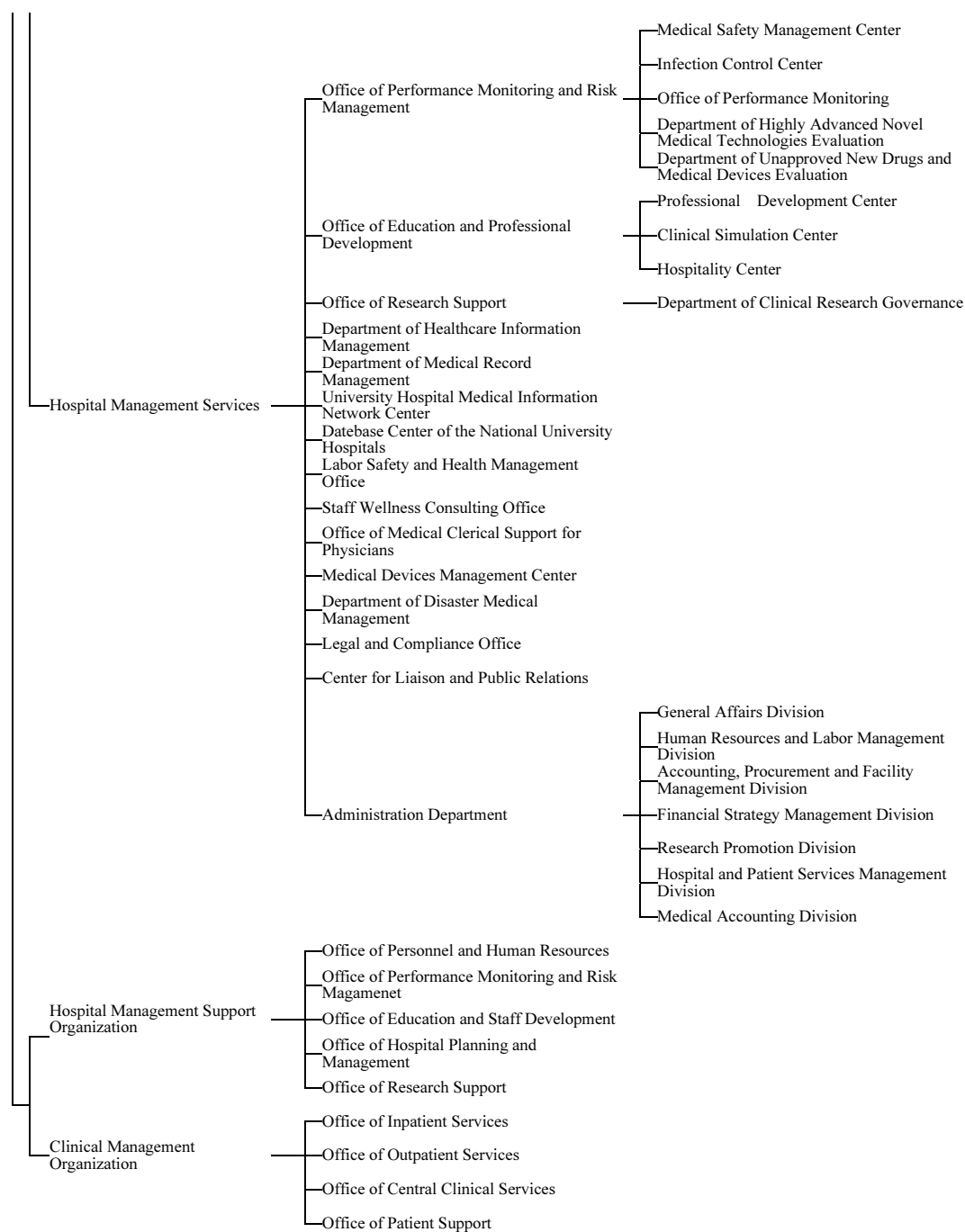












Teaching, Research, Secretarial and Administrative Staffs

Chief Members of Administration

Dean, Graduate School of Medicine (Dean, Faculty of Medicine)	Masaomi Nangaku
Chairman, School of Health Sciences and Nursing	Daisuke Nishi
Director, Medical Library	Hideo Yasunaga
Director General, University Hospital	Sakae Tanaka
Director, Center for Disease Biology and Integrative Medicine	Haruhiko Bito
Director, International Research Center for Medical Education	Makoto Aihara
Director, Global Nursing Research Center	Noriko Yamamoto
Director, Center for Diversity in Medical Education and Research	Kiyoto Kasai

Graduate School of Medicine

Molecular Cell Biology

Department of Cell Biology and Anatomy	Professor	Yasushi Okada
	Professor	Masahide Kikkawa
	Professor	Shigeo Okabe
Department of Biochemistry and Molecular Biology	Professor	Noboru Mizushima
	Professor	Yukinori Okada
	Professor	Hiroki Kurihara
	Professor	Radostin Stoyanov Danev

Functional Biology

Department of Physiology	Professor	Kenichi Ohki
	Professor	Masanori Matsuzaki
Department of Pharmacology	Professor	Kenzo Hirose
	Professor	Hiroki Ueda

Pathology, Immunology and Microbiology

Department of Pathology	Professor	Tetsuo Ushiku
	Professor	Yasuhiro Yamada
Department of Microbiology	Professor	Makoto Takeda
	Professor	Takeya Tsutsumi
Department of Immunology	Professor	Hiroshi Takayanagi

Radiology and Biomedical Engineering

Department of Radiology	Professor	Osamu Abe

Department of Biomedical Engineering	Professor	Yasuteru Urano
	Professor	Katsutoshi Oda
Neuroscience		
Department of Basic Neuroscience	Professor	Takeshi Iwatsubo
	Professor	Haruhiko Bito
Department of Integrative Medical Neuroscience		
Department of Clinical Neuroscience	Professor	Kiyoto Kasai
	Professor	Tatsushi Toda
	Professor	Nobuhito Saito
Social Medicine		
Department of Occupational, Environmental and Preventive Medicine	Professor	Shumpei Ishikawa
	Professor	Takahiro Higashi
Department of Forensic Medicine, and Medical Informatics and Economics	Professor	Hirotaro Iwase
	Professor	Kazuhiko Ohe
Internal Medicine		
Department of Medicine I	Professor	Norihiko Takeda
	Professor	Hidenori Kage
	Professor	Mitsuhiro Fujishiro
	Professor	Masaomi Nangaku
Department of Medicine II	Professor	Toshimasa Yamauchi
	Professor	Mineo Kurokawa
	Professor	Keishi Fujio
	Professor	Takeya Tsutsumi
Department of Clinical Laboratory Medicine and Pathology	Professor	Makoto Kurano
	Professor	Hitoshi Okazaki
Reproductive, Developmental and Aging Science		
Department of Obstetrics and Gynecology	Professor	Yasushi Hirota
	Professor	Yutaka Osuga
Department of Pediatric Sciences	Professor	Motohiro Kato
	Professor	Jun Fujishiro
Department of Aging Sciences	Professor	Masahiro Akishita
Surgical Sciences		
Department of Surgery	Professor	Masaaki Sato
	Professor	Minoru Ono
	Professor	Yasuyuki Seto
	Professor	Kiyoshi Hasegawa
	Professor	Haruki Kume
	Professor	Soichiro Ishihara

Department of Sensory and Motor System Medicine	Professor	Shinichi Sato
	Professor	Mutsumi Okazaki
	Professor	Kazuto Hoshi
	Professor	Sakae Tanaka
	Professor	Makoto Aihara
	Professor	Kenji Kondo
Department of Vital Care Medicine	Professor	Toru Ogata
	Professor	Kanji Uchida
	Professor	Kento Doi
Health Sciences and Nursing		
Department of Health Sciences	Professor	Daisuke Nishi
	Professor	Yutaka Matsuyama
	Professor	Hideki Hashimoto
Department of Preventive and Administrative Nursing	Professor	Mari Ikeda
Department of Clinical Nursing	Professor	Noriko Yamamoto
	Professor	Megumi Haruna
	Professor	Daisuke Nishi
	Professor	Gojiro Nakagami
International Health		
Department of International Social Medicine	Professor	Masahiro Hashizume
Department of International Biomedical Sciences	Professor	Akihiro Fujimoto
	Professor	Meng Ling Moi
	Professor	Masahiro Umezaki
	Professor	Tomoyoshi Nozaki
School of Public Health		
Department of Epidemiology and Health Sciences	Professor	Yutaka Matsuyama
	Professor	Kentaro Murakami
	Professor	Hideo Yasunaga
	Professor	Takahiro Kiuchi
Department of Behavioral Health Sciences	Professor	Daisuke Nishi
	Professor	Hideki Hashimoto
Department of Health Services Sciences	Professor	Takahiro Higashi
	Professor	Kazuhiko Ohe
	Professor	Hiroshi Oyama
	Professor	Hiroto Iwase
Center for Disease Biology and Integrative Medicine		
Laboratory of Molecular Biomedicine for Pathogenesis		
Laboratory of Structural Physiology		
Laboratory of Biomedical Equipment and Biomaterials		

Laboratory of Clinical Biotechnology	Professor	Ungil Chung
Laboratory of Microenvironmental and Metabolic Health Sciences	Professor	Makoto Murakami
Laboratory of Animal Resources	Professor	Atsu Aiba
Laboratory of Molecular Radiology		
Division of Research Resources and Support		
International Research Center for Medical Education	Professor	Masato Eto
Global Nursing Research Center		
Center for Diversity in Medical Education and Research	Associate Professor	Yoshihiro Satomura
Medical Library	Professor	Hideo Yasunaga
International Academic Affairs	Professor	Shinichi Sato
Medical Scientist Training Program	Professor	Shumpei Ishikawa
Museum of Health and Medicine	Professor	Kazuhiko Ohe
Office for Human Research Studies	Professor	Masahiro Akishita
Life Sciences Core Facility	Professor	Masahide Kikkawa
Office for Clinical Practice and Medical Education	Professor	Masato Eto
Promotion of CPC Education and General Integrative Medicine	Lecturer	Masako Ikemura
Endowed Departments		
Artificial Intelligence and Digital Twin Development in Healthcare	Project professor	Kengo Miyo
Science for Joint Reconstruction	Project professor	Toru Moro
Department of Bone & Cartilage Regenerative Medicine	Project Associate professor	Yasunori Omata
Department of Osteoimmunology	Project Associate professor	Kazuo Okamoto
Computational Diagnostic Radiology and Preventive Medicine	Project Professor	Takeharu Yoshikawa
Department of Home Care Medicine	Project Professor	Takashi Yamanaka
Therapeutic Strategy for Heart Failure	Project Associate professor	Eisuke Amiya
Department of Biostatistics and Bioinformatics	Project Professor	Daisuke Koide
Department of Advanced Cardiology	Project Associate Professor	Katsuhito Fujiu
Laboratory for Advanced Research on Pathophysiology of Metabolic Diseases	Project Associate Professor	Miki Iwabu
Department of Advanced Clinical Science and Therapeutics	Project Associate professor	Mutsuo Harada
Department of Immunotherapeutics	Project Professor	Kazuhiro Kakimi
Research on Cell Therapy of Regenerative Medicine	Project Associate Professor	Dehua Chang
Comprehensive radiation oncology	Project Professor	Keiichi Nakagawa
Department of Frontier Cardiovascular Science	Project professor	Issei Komuro
Clinical application for Development of Therapy for Rare and Intractable Diseases	Project Associate professor	Kazuki Taoka

Social Cooperation Program

Healthcare Quality Assessment	Project Professor	Hiroaki Miyata
Department of Next-Generation Pathology Information Networking	Project Professor	Takeshi Sasaki
Department of Prevention of Diabetes and Lifestyle-Related Diseases	Project Associate professor	Satoko Yamaguchi
Department of Health Services Research	Project Lecturer	Atsushi Miyawaki
Chronic Kidney Disease Pathophysiology	Project Professor	Reiko Inagi
Department of Functional Genomics and Immunological Diseases	Project Associate professor	Tomohisa Okamura
Department of Lipidomics	Project Professor	Yoshiya Oda
Tissue stem cell / life dentistry	Project Professor	Makoto Komura
Department of Eat-loss Medicine	Project Associate professor	Kazumichi Yonenaga
Department of Preventive Medicine for Locomotive Organ Disorders	Project Professor	Noriko Yoshimura
Next-Generation Precision Medicine Development Laboratory	Project Associate professor	Kousuke Watanabe
Department of Pain & Palliative Medical Sciences	Project Associate professor	Maiko Hasegawa
Department of Retinal Biology and Pathology	Project Associate Professor	Toshiro Iwagawa
Medical information engineering	Project Associate professor	Taichi Kin
Laboratory for cryo-electron microscopy	Project Associate professor	Chieko Saito
Department of Digital Mental Health	Project Professor	Norito Kawakami
Department of Cellular and Tissue Communication	Project Professor	Jun Yamashita
Clinical stem cell biology	Project Professor	Atsuhiko Hikita
Department of Precision Medicine Neurology	Project Associate professor	Jun Mitsui
Department of Real-world Evidence	Project Associate professor	Yusuke Sasabuchi
Next-generation Endoscopic Computer Vision	Project Associate professor	Yosuke Tsuji
Department of Healthcare economics and Health policy	Project Associate Professor	Yoshiki Niimi
Department of Clinical Cannabinoid Research	Project Associate Professor	Ayumi Yoshizaki
Division of Musculoskeletal AI System Development	Project Associate Professor	Hiroyuki Oka
Therapeutic Development for Intractable Bone Diseases	Project Associate Professor	Nobuaki Ito

University Hospital**Clinical Services****•Department of Internal Medicine**

General Internal Medicine	Head	Tatsuhi Toda
Cardiovascular Medicine	Head	Norihiko Takeda
Respiratory Medicine	Head	Hidehiko Kage
Gastroenterology	Head	Mitsuhiro Fujishiro
Nephrology and Endocrinology	Head	Masaomi Nangaku
Diabetes and Metabolic Medicine	Head	Toshimasa Yamauchi
Hematology and Oncology	Head	Mineo Kurokawa
Allergy and Rheumatology	Head	Keishi Fujio
Infectious Diseases	Head	Takeya Tsutsumi
Neurology	Head	Tatsushi Toda
Geriatric Medicine	Head	Masahiro Akishita
Psychosomatic Medicine	Head	Kazuhiro Yoshiuchi

•Department of Surgery

General Surgery	Head	Soichiro Ishihara
Stomach and Esophagus Surgery	Head	Yasuyuki Seto
Colon and Rectal Surgery	Head	Soichiro Ishihara
Hepato-Biliary-Pancreatic Surgery	Head	Kiyoshi Hasegawa
Vascular Surgery	Head	Soichiro Ishihara
Breast and Endocrine Surgery	Head	Masahiko Tanabe
Artificial Organ and Transplantation Surgery	Head	Kiyoshi Hasegawa
Cardiovascular Surgery	Head	Minoru Ono
Thoracic Surgery	Head	Masaaki Sato
Neurosurgery	Head	Nobuhito Saito
Anesthesiology and Pain Relief Center	Head	Kanji Uchida
Urology and Andrology	Head	Haruki Kume
Gynecologic Surgery	Head	Yutaka Ohsuga

•Department of Sensory and Motor System Medicine

Dermatology	Head	Shinichi Sato
Ophthalmology	Head	Makoto Aihara
Orthopaedic Surgery and Spinal Surgery	Head	Sakae Tanaka
Otorhinolaryngology and Head and Neck Surgery	Head	Kenji Kondo
Rehabilitation Medicine	Head	Toru Ogata
Plastic, Reconstructive and Aesthetic Surgery	Head	Mutsumi Okazaki
Oral-Maxillofacial Surgery and Orthodontics	Head	Kazuto Hoshi

•Department of Pediatrics, Perinatal and Women's Medicine

Pediatrics	Head	Motohiro Kato
Pediatric Surgery	Head	Jun Fujishiro
Obstetrics and Gynecology	Head	Yasushi Hirota

•Department of Neuropsychiatry

Neuropsychiatry	Head	Kiyoto Kasai

•Department of Radiology

Radiology	Head	Osamu Abe

•Department of Emergency and Critical Care Medicine

Emergency and Critical Care Medicine	Head	Kento Doi

•Department of Medical Oncology

Clinical Oncology	Head	Mitsuhiro Fujishiro

•Department of Cross-Sectional Services

Advanced Medical Center for Heart Failure	Head	Masaru Hatano
Center for Cardiac Arrhythmias and Electrophysiology	Head	Katsuhito Fujiu
Marfan Syndrome Center	Head	Norifumi Takeda
Epilepsy Center	Head	Yuichiro Shirota
Dementia Center	Head	Tatsushi Toda
Scleroderma Center	Head	Hayakazu Sumida
Lupus Center	Head	Keishi Fujio
Osteoporosis Center	Head	Taku Saito
Center for Female Pelvic Medicine and Reconstructive Surgery	Head	Yutaka Osuga
Spine Center	Head	Yasushi Oshima
Department of Clinical Genomics	Head	Katsutoshi Oda
Department of Child Psychiatry	Head	Yukiko Kano
Children, AYA and Family Centered Mental Care Center	Head	Yukiko Kano
Department of Pain and Palliative Medicine	Head	Masahiko Sumitani

Central Clinical Services

Pharmaceutical Department	Head	Tappei Takada
Department of Clinical Laboratory	Head	Makoto Kurano
Department of Blood Transfusion	Head	Hitoshi Okazaki
Department of Pathology	Head	Tetsuo Ushiku
Department of Infection Control and Prevention	Head	Takeya Tsutsumi
Radiology Center	Head	Osamu Abe
Rehabilitation Center	Head	Toru Ogata
Surgical Center	Head	Kazuhiko Fukatsu
Central Supply Service	Head	Kazuhiko Fukatsu
Department of Medical Engineering	Head	Kento Doi

Department of Endoscopy and Endoscopic Surgery	Head	Yosuke Nakai
Department of Hemodialysis and Apheresis	Head	Masaomi Nangaku
Critical Care and Emergency Medical Center/ER	Head	Kento Doi
Department of Intensive Care Unit	Head	Kento Doi
Department of Pediatric and Neonatal Intensive Care Unit	Head	Naoto Takahashi
Perinatal Center	Head	Yasushi Hirota
Children's Medical Center	Head	Motohiro Kato
Department of Outpatient Chemotherapy Unit	Head	Mitsuhiro Fujishiro
Cancer Center	Head	Narikazu Boku
Immune-Mediated Diseases Therapy Center	Head	Hiroko Kanda
Organ Transplantation Center	Head	Minoru Ono
Tissue Bank	Head	Sumihito Tamura
Department of Corneal Transplantation	Head	Takashi Miyai
Department of Cell Therapy and Transplantation Medicine	Head	Mineo Kurokawa
Admission and Discharge Center	Head	Keita Okada
Perioperative Assessment and Care Center	Head	Kanji Uchida
Clinical Nutrition Center	Head	Kazuhiko Fukatsu
Swallowing Center	Head	Rumi Ueha
International Medical Center	Head	Sumihito Tamura
Center for Epidemiology and Preventive Medicine	Head	Nobutake Yamamichi
Center for International Preventive Medicine	Head	Yoko Iizuka
Cancer Board	Head	Haruki Kume
Vascular Board	Head	Katsuyuki Hoshina
Hip Fracture Board	Head	Taro Kojima
Palliative Care Consultation Team	Head	Masahiko Sumitani
Nutrition Support Team	Head	Kazuhiko Fukatsu
Medical Community Network and Discharge Supporting Center	Head	Masahiko Sumitani
Cancer Resource Center	Head	Sachiyo Nomura
Patient Relations and Clinical Ethics Center	Head	Yoshiyuki Takimoto

Clinical Research Services

Clinical Research Promotion Center	Head	Takashi Moritoyo
22nd Century Medical and Research Center	Head	Yutaka Osuga
Department of Tissue Engineering	Head	Kazuto Hoshi
Cooperative Unit of Medicine and Engineering Research	Head	Minoru Ono
Translational Research Center	Head	Yutaka Osuga
Genomic Research Support Center	Head	Yutaka Osuga
Unit for Early and Exploratory Clinical Development	Head	Takeshi Iwatsubo
BioResource Center	Head	Tetsuo Ushiku

Center for Brain Imaging in Health and Diseases	Head	Kiyoto Kasai

Hospital Management Services

Medical Safety Management Center	Head	Tomotaka Yamamoto
Infection Control Center	Head	Takeya Tsutsumi
Office of Performance Monitoring	Head	Tomotaka Yamamoto
Department of Highly Advanced Novel Medical Technologies Evaluation	Head	Haruki Kume
Department of Unapproved New Drugs and Medical Devices Evaluation	Head	Kanji Uchida
General Education Center	Head	Masato Eto
Clinical Simulation Center	Head	Masato Eto
Department of Clinical Research Governance	Head	Yutaka Osuga
Department of Healthcare Information Management	Head	Yoshimasa Kawazoe
Department of Medical Record Management	Head	Shinichiro Yokota
University Hospital Medical Information Network Center	Head	Takahiro Kiuchi
Labor Safety and Health Management Office	Head	Tomotaka Yamamoto
Staff Wellness Consulting Office	Head	Kiyoto Kasai
Office of Medical Clerical Support for Physicians	Head	Haruki Kume
Medical Devices Management Center	Head	Kento Doi
Department of Disaster Medical Management	Head	Kento Doi
Legal and Compliance Office	Head	Kanji Uchida
Center for Liaison and Public Relations	Head	Kiyoto Kasai

Hospital Management Support Organization

Office of Personnel and Human Resources	Head	Kiyoto Kasai
Office of Performance Monitoring and Risk Management	Head	Kanji Uchida
Office of Education and Staff Development	Head	Yutaka Osuga
Office of Hospital Planning and Management	Head	Haruki Kume
Office of Research Support	Head	Yutaka Osuga

Clinical Management Organization

Office of Inpatient Services	Head	Mitsuhiro Fujishiro
Office of Outpatient Services	Head	Toshimasa Yamauchi
Office of Central Clinical Services	Head	Masahiko Sumitani
Office of Patient Support	Head	Kiyoto Kasai

The University of Tokyo,
Graduate School of Medicine

Molecular Cell Biology

1. Cell Biology and Anatomy

Department of Cell Biology

Professor

Yasushi Okada, M.D.,Ph.D.

Lecturer

Kazuho Ikeda, Ph.D.

Research Associate

Akira Takai, Ph. D.

Takanobu Katoh, Ph. D.

Homepage <https://www.okada-lab.phys.s.u-tokyo.ac.jp/en/>

Introduction and Organization

Our laboratory is one of the laboratories in Department of Cell Biology and Anatomy, since the reorganization of School of Medicine in 1997. The current lab was established in 2020 when Yasushi Okada was appointed as a professor.

Currently the lab members include: Yasushi Okada (professor), Kazuho Ikeda (Lecturer), Akira Takai and Takanobu Katoh (research associates).

Teaching activities

Our laboratory, together with other laboratories in this department, is in charge of teaching following courses:

- 1) Gross Anatomy for medical students.
- 2) Cell Biology and Histology for medical students.
- 3) Special training (Free Quarter) for medical students.
- 4) Advance cell biology course for graduate students.

Research activities

Our primary goal is to answer the very basic question “What is life”. To answer this question, we are trying to fill the gap between the world of molecules and the world of living cells. Direct measurement of

molecules in living cells would serve as a basic technology to fill this gap. Thus, we have been working on the development of the technologies for the visualization and non-invasive measurement of the molecular processes in living cells. High-speed, super-resolution live-cell imaging and single-molecule measurement in living cells are the two main technologies we develop.

By using these technologies, we are trying to understand the regulatory mechanisms of motor proteins during axonal transport. Despite the many studies in the past decades by our group and others, it is still unclear how the biophysical properties of motor proteins are related to their biological functions. For example, a point mutation in kinesin-1 can cause hereditary spastic paraplegia, but it is unclear why this mutation selectively affects neurons in the longest tract in the aged patients.

Through these studies and development, we have realized the importance of the cellular states, and our microscope technologies can also be applied to the measurement of the cellular states. Thus, we have proposed a project for the visualization, prediction, and control of cellular states.

References

1. Ando R, Shimozone S, Ago H, Takagi M, Sugiyama M, Kurokawa H, Hirano M, Niino Y, Ueno G, Ishidate F, Fujiwara T, **Okada Y**, Yamamoto M, Miyawaki A. StayGold variants for molecular fusion and membrane-targeting applications. *Nat Methods* 21: 648-656, 2024.
2. Ishikawa S, Iwanaga Y, Ueyama T, Li X, Hojo H, Fujinaga I, Katashima T, Saito T, **Okada Y**, Chung U, Sakumichi N, Sakai T. Percolation-induced gel–gel phase separation in a dilute polymer network. *Nat Mater* 22: 1564-1570, 2023.
3. Okamoto K, Fujita H, **Okada Y**, Shinkai S, Onami S, Abe K, Fujimoto K, Sasaki K, Shioi G, Watanabe TM. Single-molecule tracking of Nanog and Oct4 in living mouse embryonic stem cells uncovers a feedback mechanism of pluripotency maintenance. *EMBO J* 42: e112305, 2023.
4. Fukuda T, Furukawa K, Maruyama T, Yamashita SI, Noshiro D, Song C, Ogasawara Y, Okuyama K, Alam JM, Hayatsu M, Saigusa T, Inoue K, Ikeda K, Takai A, Chen L, Lahiri V, **Okada Y**, Shibata S, Murata K, Klionsky DJ, Noda NN, Kanki T. The mitochondrial intermembrane space protein mitofissin drives mitochondrial fission required for mitophagy. *Mol Cell* 83: 2045-2058, 2023.
5. Katoh TA, Omori T, Ishikawa T, **Okada Y**, Hamada H. Biophysical Analysis of Mechanical Signals in Immotile Cilia of Mouse Embryonic Nodes Using Advanced Microscopic Techniques. *Bio Protoc* 13: e4715, 2023.
6. Fukuda K, Shimi T, Shimura C, Ono T, Suzuki T, Onoue K, Okayama S, Miura H, Hiratani I, Ikeda K, **Okada Y**, Dohmae N, Yonemura S, Inoue A, Kimura H, Shinkai Y. Epigenetic plasticity safeguards heterochromatin configuration in mammals. *Nucleic Acids Res* 51: 6190-6207, 2023.
7. Nozaki T, Shinkai S, Ide S, Higashi K, Tamura S, Shimazoe MA, Nakagawa M, Suzuki Y, **Okada Y**, Sasai M, Onami S, Kurokawa K, Iida S, Maeshima K. Condensed but liquid-like domain organization of active chromatin regions in living human cells. *Science Advances* 9: eadf1488, 2023.
8. Katoh TA, Omori T, Mizuno K, Sai X, Minegishi K, Ikawa Y, Nishimura H, Itabashi T, Kajikawa E, Hiver S, Iwane AH, Ishikawa T, **Okada Y**, Nishizaka T, Hamada H. Immotile cilia mechanically sense the direction of fluid flow for left-right determination. *Science* 379: 66-71, 2023.
9. Takao D, Kyunai YM, **Okada Y**, Satoh A. A Primer on Deep Learning-Based Cellular Image Classification of Changes in the Spatial Distribution of the Golgi Apparatus After Experimental Manipulation. *Methods Mol Biol* 2557: 275-285, 2023.

Department of Cell Biology & Anatomy (Structural Biology)

Professor

Masahide Kikkawa, M.D., Ph.D.

Lecturer

Haruaki Yanagisawa, Ph.D.

Research Associate

Tsukasa Makino, Ph. D, Hiroshi Yamaguchi, Ph. D

Homepage <http://structure.m.u-tokyo.ac.jp>

Introduction and Organization

Our laboratory is one of the laboratories in Department of Cell Biology and Anatomy. Since the reorganization of School of Medicine in 1997, the lab was named as “Structural Biology”. The current lab was established in 2009 when Masahide Kikkawa was appointed as a professor.

Currently the lab members include: Masahide Kikkawa (professor), Haruaki Yanagisawa (Lecturer), Tsukasa Makino, Hiroshi Yamaguchi (research associates), Jiang Xuguang, An Jiancheng (Post doctoral fellows), Yuma Tani, Yuqing Liu and Jingfei Yang (graduate students), Takeru Mutoh, Yoshitaka Nakayama (MSTP students), Akiko Oosakaya, Sakamaki Yoichi, Toshie Furuya, Miku Takagishi, Tony Wang and Yoriko Akuzawa (Technical assistant), and Mikako Yanagiuchi and Ai Naruse (Assistant clerk).

Teaching activities

Our lab, together with Kanai and Okabe’s lab, is in charge of teaching following courses:

- 1) Gross Anatomy for medical students.
- 2) Cell Biology and Histology for medical students.
- 3) Special training (Free Quarter) for medical

students.

- 4) Advance cell biology course for graduate students.

Research activities

Our lab focuses on the structure and function of epithelial structures, especially eukaryotic flagella/cilia. Flagella/cilia are both “propeller” and “antenna” of cells, whose diameter is about 250 nm. From recent studies, it is becoming clear that flagella/cilia are involved in various important cell functions.

To study the functions of flagella/cilia, we employ various imaging techniques, including cryo-electron microscopy and 3D-tracking microscope in combination with genetic manipulations.

Cryo-electron microscopy and cryo-electron tomography

One of our strengths is in high-resolution cryo-electron microscopy (cryo-EM). This technique enables preserving biological samples by quickly freezing them and observing the frozen samples without staining. Using electron microscopy, we are able to obtain nano-meter resolution of macro-molecular complexes such as axonemes. We have been developing new techniques, such as asymmetric helical reconstruction and Ruby-Helix software.

A new project for cryo-electron microscopy started in October 2017 with a grant from AMED (Japan Agency for Medical Research and Development). This project is intended to make cryo-EM techniques available to many biological/medical researchers. New state-of-the-art cryo-electron microscopes are used by many researchers in Japan, including external users.

Model Organism

Our lab currently uses *Chlamydomonas*, zebrafish, and mice as a model organism for studying cilia/flagella. To identify molecules that are involved in regulating dynein, we use various genetic tools, including classical mutagenesis, siRNA.

In addition, we are also developing 3D-tracking microscopy in collaboration with Dr. Oku in Department of Engineering. We are trying to track *Chlamydomonas* cells and simultaneously record flagella movement to elucidate the mechanism of flagella regulation.

References

- [1] Bui, H.B., Watanabe, S., Nomura, N., Liu, K., Uemura, T., Inoue, M., Tsutsumi, A., Fujita, H., Kinoshita, K., Kato, Y., Iwata, S., Kikkawa, M., Inaba, K., 2023. Cryo-EM structures of human zinc transporter ZnT7 reveal the mechanism of Zn²⁺ uptake into the Golgi apparatus. *Nat Commun* 14, 4770.
- [2] Kikkawa, M., 2023. A quest to unravel the role of the stalk and microtubule-binding domain of axonemal dyneins. *FEBS Lett* 597, 2147–2148.
- [3] Kubo, T., Tani, Y., Yanagisawa, H.-A., Kikkawa, M., Oda, T., 2023. α - and β -tubulin C-terminal tails with distinct modifications are crucial for ciliary motility and assembly. *J Cell Sci* 136, jcs261070.
- [4] Sakuragi, T., Kanai, R., Otani, M., Kikkawa, M., Toyoshima, C., Nagata, S., 2024. The role of the C-terminal tail region as a plug to regulate XKR8 lipid scramblase. *J Biol Chem* 300, 105755.
- [5] Shen, H.K., Morishita, K., Hashim, P.K., Okuro, K., Kashiwagi, D., Kimura, A., Yanagisawa, H., Kikkawa, M., Niwa, T., Taguchi, H., Aida, T., 2023. ATP-Responsive Nanoparticles Covered with Biomolecular Machine “Chaperonin GroEL.” *Angew Chem Int Ed Engl* 62, e202304894.
- [6] Takeda, H., Busto, J.V., Lindau, C., Tsutsumi, A., Tomii, K., Imai, K., Yamamori, Y., Hirokawa, T., Motono, C., Ganesan, I., Wenz, L.-S., Becker, T., Kikkawa, M., Pfanner, N., Wiedemann, N., Endo, T., 2023. A multipoint guidance mechanism for β -barrel folding on the SAM complex. *Nat Struct Mol Biol* 30, 176–187.
- [7] Yanagisawa, H., Kita, Y., Oda, T., Kikkawa, M., 2023. Cryo-EM elucidates the uroplakin complex structure within liquid-crystalline lipids in the porcine urothelial membrane. *Commun Biol* 6, 1018.

Department of Cytoarchitectonics

Lecturer

Yosuke Tanaka, M.D., Ph.D.

Homepage <http://cb.m.u-tokyo.ac.jp/>; <https://www.yosuket1969.com/>

Teaching activities

Our teaching responsibility is as follows:

- I.
 - 1) Lecture on Cell Biology, Developmental Biology, Histology and Neurocytology.
 - 2) Lecture on Gross Anatomy and Neuroanatomy to medical students and students of other faculties
- II.
 - 1) Laboratory course of Gross Anatomy and Neuroanatomy.
 - 2) Laboratory course of Histology and Histology of the Central Nervous System.

to medical students and students of other faculties.

In addition, we offer a special training course (free quarter) of various kinds of molecular cell biology techniques such as immunocytochemistry, electron microscopy, biochemistry, molecular biology, biophysics, and cellular and molecular neurobiology technique to medical students.

Research activities

Our research field covers the molecular cell biology of the cytoskeleton. We focus on the molecular mechanisms of cell morphogenesis and intracellular transports.

Our laboratory studies molecular architecture, dynamics and function of the neuronal cytoskeleton using various new molecular cell biological approaches including new electron microscopy such as the quick freeze deep etch electron microscopy, cryo-electron microscopy at atomic resolution, and cryo-ultramicrotomy, biochemistry, immunocytochemistry, molecular biology, molecular genetics such as gene targeting and transgenic mouse approaches, molecular biophysics and structure biology including

X ray crystallography and cryoelectron microscopy.

In this way we can study structure, dynamics and functions of cytoskeleton from gene to cell, tissue and whole body.

Nerve cells as units of complicated neuronal networks in the brain develop very polarized morphology composed of dendrites, cell body and a long axon along the direction of impulse propagation. The neuronal cytoskeleton plays three major important roles.

- 1) It provides dynamic frameworks for neurite extension and maintenance.
- 2) It provides structural bases for organelle transports in the cells. Namely it works as rails and motor molecules to transport materials from cell center to periphery and from periphery to cell center.
- 3) It very importantly regulates release processes of transmitters and also contributes to anchor receptors at the postsynaptic sites.

Our laboratory studies molecular architecture, dynamics and function of the cytoskeleton focusing on these three major roles.

To study these molecular mechanisms, we use new molecular cell biological approaches including electron microscopy of molecular resolution, biochemistry, biophysics, molecular biology and molecular genetics and X-ray crystallography.

References

1. **Tanaka Y**, Morozumi A, Hirokawa N. Nodal flow transfers polycystin to determine mouse left-right asymmetry. **Dev Cell**. 2023 Aug 21; 58(16):1447-1461.e6.
2. Wan Y, Morikawa M, Morikawa M, Iwata S, Naseer MI, Ahmed Chaudhary AG, **Tanaka Y**,

Hirokawa N. KIF4 regulates neuronal morphology and seizure susceptibility via the PARP1 signaling pathway. **J Cell Biol.** 2023 Feb 6; 222(2):e202208108.

3. Jiang X, Ogawa T, Yonezawa K, Shimizu N, Ichinose S, Uchihashi T, Nagaike W, Moriya T, Adachi N, Kawasaki M, Dohmae N, Senda T, Hirokawa N. The two-step cargo recognition mechanism of heterotrimeric kinesin. **EMBO Rep.** 2023 Nov 6; 24(11):e56864.

Department of Cellular Neurobiology

Professor

Shigeo Okabe, M.D., Ph.D.

Research Associate

Yutaro Kashiwagi, Ph.D., Hisato Maruoka, Ph.D., Hirotaka Asai, Ph.D.

Homepage <http://synapse.m.u-tokyo.ac.jp/>

Introduction and Organization

The Department of Cellular Neurobiology was initially established as the Neuroanatomy department of former Brain Institute of Medical School of Imperial University of Tokyo in 1936. Since the structural reconstruction of the School of Medicine in 1997, this department became one of the departments of Cell Biology and Anatomy of the Graduate School of Medicine. Professor Shigeo Okabe had currently organized this department since September 2007. The department is constituted of 17 members.

Education

For medical students, our department takes the following lectures and courses.

1. Cell Biology, Histology, and Neurocytology
2. Gross Anatomy and Neuroanatomy.
3. Free Quarter.

For graduate students, we offer the following lectures and seminars.

1. Cellular Neurobiology.
2. Cell Biology and Histology.
3. Discussion seminars and progress reports of the experiment.
4. Joint seminar with other departments

Research

Brain functions, which are dependent on mutual communication of a tremendous number of neuronal

cells, regulate the behavior of animals and humans. The main structure specifically differentiated for information exchange between neurons, is called "synapse." Long-term maintenance of synaptic properties underlies the stability and reproducibility of behavior in responses to external stimuli. In turn, alterations of synaptic properties are thought to be the basis of behavioral change in the course of animal development and also after learning. Therefore, synapses should be stabilized for the long term to realize fidelity of various animal behaviors, but also should be altered rapidly when animals adapt to a new environment. The molecular basis of this dichotomy, which is unique to synapses, is the main interest of our laboratory.

Synapse is the site of signal transmission between neurons. Most of the synapses are formed during the early development, and after that, they become stable after the intensive pruning. We are interested in how synapse is developed and maintained. The postsynaptic densities (PSDs) are protein-dense structures which are located closely to postsynaptic membranes. PSDs include a variety of receptors, scaffolding proteins, and signaling molecules. We focus on PSD proteins and examine their roles in synapse development.

Two-photon excitation microscopy allows imaging of the living brain. We examine synapse remodeling in vivo by observing the postsynaptic structures and PSD proteins tagged by fluorescent probes. We are also investigating synapse pathology in developmental

disorders by using mouse models. For both in vitro and in vivo analyses of synapses, the development of new imaging technologies is essential. Our laboratory has made a significant contribution to the quantitative and high-resolution imaging of synapse dynamics.

Publications

1. Nozawa O, Miyata M, Shiotani H, Kameyama T, Komaki R, Shimizu T, Kuriu T, Kashiwagi Y, Sato Y, Koebisu M, Aiba A, **Okabe S**, Mizutani K, Takai Y. Necl2/3-mediated mechanism for tripartite synapse formation.
Development. 2023 Feb 15;150(4):dev200931. doi: 10.1242/dev.200931.
2. Urata S, **Okabe S**. Three-dimensional mouse cochlea imaging based on the modified Sca/eS using confocal microscopy.
Anat Sci Int. 2023 Jul;98(3):309-317. doi: 10.1007/s12565-023-00703-z.
3. Kamei R, **Okabe S**. In vivo imaging of the phagocytic dynamics underlying efficient clearance of adult-born hippocampal granule cells by ramified microglia.
Glia. 2023 Aug;71(8):2005-2023. doi: 10.1002/glia.24379.
4. Shima Y, Sasagawa S, Ota N, Oyama R, Tanaka M, Kubota-Sakashita M, Kawakami H, Kobayashi M, Takubo N, Ozeki AN, Sun X, Kim YJ, Kamatani Y, Matsuda K, Maejima K, Fujita M, Noda K, Kamiyama H, Tanikawa R, Nagane M, Shibahara J, Tanaka T, Rikitake Y, Mataga N, Takahashi S, Kosaki K, Okano H, Furihata T, Nakaki R, Akimitsu N, Wada Y, Ohtsuka T, Kurihara H, Kamiguchi H, **Okabe S**, Nakafuku M, Kato T, Nakagawa H, Saito N, Nakatomi H. Increased PDGFRB and NF- κ B signaling caused by highly prevalent somatic mutations in intracranial aneurysms.
Sci Transl Med. 2023 Jun 14;15(700):eabq7721. doi: 10.1126/scitranslmed.abq7721..
5. Hagihara H, Shoji H, Hattori S, Sala G, Takamiya Y, Tanaka M, Ihara M, Shibutani M, Hatada I, Hori K, Hoshino M, Nakao A, Mori Y, **Okabe S**, Matsushita M, Urbach A, Katayama Y, Matsumoto A, Nakayama KI, Katori S, Sato T, Iwasato T, Nakamura H, Goshima Y, Raveau M, Tatsukawa T, Yamakawa K, Takahashi N, Kasai H, Inazawa J, Nobuhisa I, Kagawa T, Taga T, Darwish M, Nishizono H, Takao K, Sapkota K, Nakazawa K, Takagi T, Fujisawa H, Sugimura Y, Yamanishi K, Rajagopal L, Hannah ND, Meltzer HY, Yamamoto T, Wakatsuki S, Araki T, Tabuchi K, Numakawa T, Kunugi H, Huang FL, Hayata-Takano A, Hashimoto H, Tamada K, Takumi T, Kasahara T, Kato T, Graef IA, Crabtree GR, Asaoka N, Hatakama H, Kaneko S, Kohno T, Hattori M, Hoshiba Y, Miyake R, Obi-Nagata K, Hayashi-Takagi A, Becker LJ, Yalcin I, Hagino Y, Kotajima-Murakami H, Moriya Y, Ikeda K, Kim H, Kaang BK, Otabi H, Yoshida Y, Toyoda A, Komiyama NH, Grant SGN, Ida-Eto M, Narita M, Matsumoto KI, Okuda-Ashitaka E, Ohmori I, Shimada T, Yamagata K, Ageta H, Tsuchida K, Inokuchi K, Sassa T, Kihara A, Fukasawa M, Usuda N, Katano T, Tanaka T, Yoshihara Y, Igarashi M, Hayashi T, Ishikawa K, Yamamoto S, Nishimura N, Nakada K, Hirotsune S, Egawa K, Higashisaka K, Tsutsumi Y, Nishihara S, Sugo N, Yagi T, Ueno N, Yamamoto T, Kubo Y, Ohashi R, Shiina N, Shimizu K, Higo-Yamamoto S, Oishi K, Mori H, Furuse T, Tamura M, Shirakawa H, Sato DX, Inoue YU, Inoue T, Komine Y, Yamamori T, Sakimura K, Miyakawa T. Large-scale animal model study uncovers altered brain pH and lactate levels as a transdiagnostic endophenotype of neuropsychiatric disorders involving cognitive impairment.
Elife. 2024 Mar 26;12:RP89376. doi: 10.7554/eLife.89376.
6. **Okabe S**. Development and Application of Technology for Neural Circuit Visualization - Secondary Publication.
JMA J. 2024 Apr 15;7(2):185-189. doi: 10.31662/jmaj.2024-0019.
7. Mori D, Inami C, Ikeda R, Sawahata M, Urata S, Yamaguchi ST, Kobayashi Y, Fujita K, Arioka Y, Okumura H, Kushima I, Kodama A, Suzuki T, Hirao T, Yoshimi A, Sobue A, Ito T, Noda Y, Mizoguchi H, Nagai T, Kaibuchi K, **Okabe S**, Nishiguchi K, Kume K, Yamada K, Ozaki N. Mice with deficiency in Pcdh15, a gene associated with bipolar disorders, exhibit

significantly elevated diurnal amplitudes of locomotion and body temperature.

Transl Psychiatry. 2024 May 28;14(1):216.
doi:10.1038/s41398-024-02952-6.

Molecular Cell Biology

2. Biochemistry and Molecular Biology

Department of Molecular Biology

Professor

Noboru Mizushima, M.D., Ph.D.

Associate Professor

Ikuko Koyama-Honda, Ph.D.

Associate

Saori Yoshii, M.D., Ph.D., Tomoya Eguchi, M.D., Ph.D.

Project Lecturer

Taki Nishimura, Ph.D.

Project Research Associate

Junichi Sakamaki, Ph.D. (~ October 2023)

Homepage <https://molbiolut.jp/en/>

Introduction and Organization

Established in 1893 as a part of Department of Physiology, this Department became independent in 1897. It was renamed Department of Biochemistry in 1927, First Department of Biochemistry in 1974, and Department of Molecular Biology in 1997, according to the creation of new related departments and the reorganization of Faculty of Medicine. This Department has been headed by seven professors, each of whom made significant contributions to the development of biochemistry, nutrition, and molecular biology in Japan.

Professor Muneo Kumagawa, who established this Biochemistry or Medical Chemistry Department for the first time in Japan, graduated from The University of Tokyo Faculty of Medicine in 1882. In 1884 he went to Germany to study in Department of Pathology, The University of Berlin headed by Dr. Rudolf Virchow under the supervision of Dr. Ernst Salkowski. After returning to Japan, he became Lecturer and was promoted to Professor of this Department. In 1908, he discovered a lack of glycogenecity in lipids, which has been firmly established besides some exceptions, and succeeded in

the purification of vitamin B1, which had been discovered by Dr. C. Eijkman in 1906. His lab produced many famous researchers, including Dr. Masahiro Sakaguchi, who developed a world-famous colorimetric method for arginine, and Dr. Takaoki Sasaki, who first succeeded in generating liver cancer with chemicals.

Professor Samuro Kakiuchi graduated from the Imperial University of Tokyo, Faculty of Medicine in 1906 and studied under Professor Kumagawa. After studying in the US, he came back to succeed the late Kumagawa. He launched the Journal of Biochemistry and founded the Japanese Society of Biochemistry. His students included Professors Kodama and Shimazono.

Professor Keizo Kodama graduated from the Imperial University of Tokyo in 1918. After studying at Cambridge University, he became Professor of Biochemistry at Kyushu Imperial University. In 1943, he took up a professorship at this Department. His research was on oxidation and reduction, and nutrition.

Professor Norio Shimazono, a graduate of the Imperial University of Tokyo Faculty of Medicine in 1928, became a professor at Niigata Medical

School. In 1952 he succeeded Professor Kodama. He studied vitamin B1/ cocarboxylase, ketoacid metabolism and hexose metabolism.

Professor Tamio Yamakawa graduated from the Imperial University of Tokyo Faculty of Medicine, and began studies at the Institute for Infectious Diseases, the University of Tokyo. He took up a professorship to succeed Professor Shimazono. He was a pioneer in glycolipid research and discovered the involvement of sialic acid in the ABO blood type antigens.

Professor Masami Muramatsu graduated from the University of Tokyo Faculty of Medicine in 1955. He began studies at the Department of Internal Medicine, and then went to Baylor College of Medicine to study under Dr. H. Busch. After coming back to Japan, he took a position at the Cancer Institute and then took up a professorship at Tokushima University School of Medicine. In 1982, he succeeded Professor Yamakawa. He studied ribosomal RNA and cloned interferon and p450 genes.

Professor Hiroto Okayama graduated from Kumamoto University School of Medicine in 1973. After taking a Ph.D. degree at Kyoto University School of Medicine, he went to Stanford University to study under Dr. P. Berg. After working at the NIH, USA, he became Professor of Molecular Genetics, at Osaka University Institute for Infectious Diseases. In 1993 he succeeded Professor Muramatsu. At Stanford and the NIH, he studied gene cloning and developed a full-length cDNA cloning method and a cDNA expression cloning vector system, and, after returning to Japan, he studied cell cycle control and cancer.

Professor Noboru Mizushima graduated from Tokyo Medical and Dental University, Faculty of Medicine in 1991. After receiving Ph.D., he studied at National Institute for Basic Biology in Okazaki and started works on autophagy in yeast and mammals at Dr. Yoshinori Ohsumi's laboratory. Taking a position as a PI at the Tokyo Metropolitan Institute of Medical Science in 2004, he started studies on the physiological roles of autophagy. He was promoted to Professor of Physiology and Cell Biology, in Graduate School and Faculty of Medicine at Tokyo Medical and Dental University in 2006, and succeeded Professor Okayama in 2012.

Research Activities

Our current study focuses on the understanding of the molecular mechanism and physiological roles of autophagy and other intracellular degradation systems. In 2022, we reported the following novel findings.

1. Molecular mechanism of autophagy

Autophagy is one of the major degradation pathways in the cell. In autophagy, intracellular components are sequestered by autophagosomes and then degraded upon fusion with lysosomes. Yeast genetic studies have identified more than 40 autophagy-related (*ATG*) genes. Many of these genes are conserved in higher eukaryotes, which allows us to perform genetic analysis of autophagy in mammals. We are currently addressing some of the central questions remaining in the autophagy field and trying to elucidate the mechanisms of (1) regulation of autophagy, (2) initiation of autophagosome formation, (3) elongation of the autophagic membrane, (4) closure, fusion, and degradation of the autophagosome (5) recognition of selective substrates. In addition, we are also working on intracellular degradation systems other than autophagy.

Autophagosome formation requires dozens of different ATG molecules, some of which bind to the membrane via amphipathic α -helices. We focused on the amphipathic α -helix of ATG3 and found that it has unique properties different from those derived from other ATG molecules. This study not only characterized the ATG3 amphiphilic α -helix, but also contribute to the elucidation of the regulatory mechanisms of other molecules. We also proposed a new method for analyzing amphiphilic α -helices using machine learning (Nishimura et al. *Sci Adv* 2023).

Autophagy is a major degradation pathway for intracellular organelles. Our laboratory has identified TEX264, an adaptor molecule involved in autophagic degradation of the endoplasmic reticulum (ER-phagy) (Chino et al. *Mol Cell* 2019). However, the short intraendoplasmic reticulum domain of TEX264 is thought to be unsuitable for recognition of abnormal proteins in

the lumen of the ER. Therefore, we searched for ER-phagy adaptors involved in the recognition of misfolded proteins in the ER lumen and found that CCPG1 is important. The ER luminal domain of CCPG1 contains multiple cargo interacting regions that directly bind to substrates. P3H4 (an ER enzyme) was also identified as an endogenous cargo for CCPG1. The physiological significance of CCPG1 in the removal of abnormal proteins in the endoplasmic reticulum will be clarified (Ishii et al. *Mol Biol Cell* 2023).

2. Physiological and pathological roles of autophagy

Using autophagosome-indicator GFP-LC3 mice and various autophagy-deficient mouse models, we have shown that autophagy is important for the maintenance of the amino acid pool during starvation and neonatal periods, preimplantation development as an amino acid supplying system, and for intracellular protein quality control to prevent neurodegeneration and tumorigenesis.

A collaborative research group including us reported in 2013 that the causative gene for the neurodegenerative disease BPAN/SENDA is WDR45 (encoding WIPI4) (Saito et al. *Nat Genet* 2013). WIPI4 belongs to the PROPPIN family, and mammals have four homologs (WIPI1-4). Using a highly sensitive and quantitative HaloTag processing assay that we developed recently, we comprehensively measured autophagy activity in various WIPI-deficient cells. We found that not only WIPI2, which was previously reported to be important for autophagy, but also WIPI3 and WIPI4 are partially required for mammalian autophagy. In addition, BPAN is a disease with two aspects: neurodevelopmental abnormalities and neurodegeneration. Analysis of disease-associated mutants suggested that autophagy defects are associated with neurodevelopmental abnormalities in BPAN, while no clear association between neurodegeneration and autophagy defects was observed. This result suggested that WIPI4 has a non-autophagic function and that defects in

non-autophagic function are responsible for neurodegeneration (Shimizu et al. *Hum Mol Genet* 2023).

Our laboratory has found that PLAAT, a cytosolic lipase, is required for large-scale organelle degradation in the lens (Morishita et al. *Nature* 2021). In this study, we identified a human disease with a mutation in PLAAT3 and found the patients show lipodystrophy. Currently, ocular manifestations are not clear (Schuermans et al. *Nat Genet* 2023).

3. Methods for monitoring autophagic activity

Measuring autophagic activity is critical to dissecting molecular mechanisms and functions of autophagy but remains challenging due to the lack of a definitive method. For example, the accumulation of autophagosomes is not necessarily caused by induction of autophagy, but also by blocking of later steps such as lysosomes. Our laboratory has developed a method for quantifying autophagy activity in cultured cells. We are currently developing a method that can be used in individual mice.

4. Autophagy-independent pathway

We reported that the Rim101-V-ATPase pathway which is involved in the extracellular alkaline stress response was identified as a regulator of yeast cell size (Shimasawa et al. *J Biol Chem* 2023).

Education

To medical students, we give lectures on biochemistry and molecular biology. General metabolism, protein synthesis, protein degradation, and metabolism of carbohydrates, amino acids, and nucleic acids are the topics in our lectures. To graduate students, the molecular biology course consisting of lectures and experiments is provided.

Publication

1. Schuermans, N., El Chehadeh, S., Hemelsoet, D., Gautheron, J., Vantyghem, M.C., Nouioua, S., Tazir, M., Vigouroux, C., Auclair, M., Bogaert, E., Dufour, S., Okawa, F., Hilbert, P., Van Doninck,

- N., Taquet, M.C., Rosseel, T., De Clercq, G., Debackere, E., Van Haverbeke, C., Cherif, F.R., Urtizberea, J.A., Chanson, J.B., Funalot, B., Authier, F.J., Kaya, S., Terryn, W., Callens, S., Depypere, B., Van Dorpe, J. Program for Undiagnosed Diseases (UD-PrOZA), Poppe, B., Impens, F., Mizushima, N., Depienne, C., J ru, I., *Dermaut, B. Loss of phospholipase PLAAT3 causes a mixed lipodystrophic and neurological syndrome due to impaired PPAR  signaling. *Nat. Genet.* 55:1929-1940 (2023).
2. Shimizu, T., Tamura, N., Nishimura, T., Saito, C., Yamamoto, H., *Mizushima, N., Comprehensive analysis of autophagic functions of WIPI family proteins and their implications for the pathogenesis of  -propeller associated neurodegeneration. *Hum Mol Genet.* 32: 2623-2637 (2023).
3. *Nishimura, T., Lazzeri, G., Mizushima, N., *Covino, R., Tooze, S. Unique Amphipathic  -helix Drives Membrane Insertion and Enzymatic Activity of ATG3. *Sci Adv* 9: eadh1281 (2023)
4. Ishii, S., Chinob, H. Ode, K.L., Kurikawa, Y., Ueda, H.R., Matsuura, A., *Mizushima, N., *Itakura, E. CCPG1 recognizes ER luminal proteins for selective ER-phagy. *Mol Biol Cell.* 34:ar29 (2023)
5. Shimasawa, M., Sakamaki, J.I., *Mizushima, N. The pH-sensing Rim101 pathway regulates cell size in budding yeast. *J. Biol. Chem.* 299: 102973 (2023)
6. Fu, J., Zhao, L., Pang, Y., Chen, H., Yamamoto, H., Chen, Y., Li, Z., Mizushima, N., *Jia H. Apicoplast biogenesis mediated by ATG8 requires the ATG12           and SNAP29 complexes in *Toxoplasma gondii*. *Autophagy* 19:1258-1276 (2023)
7. *Sakamaki, J.-i., *Mizushima, N. Ubiquitination of non-protein substrates. *Trends Cell Biol.* 33: 991-1003 (2023)
8. *Sakamaki, J.-i., *Mizushima, N. Cell biology of protein       conjugation. *Cell Struct. Funct.* 48: 99-112 (2023)
9. Liton, P.B., Boesze-Battaglia, K., Boulton, M.E., Boya, P., Ferguson, T.A., Ganley, I.G., Kauppinen, A., Laurie, G.W., *Mizushima, N., Morishita, H., Russok, R., Sadda, J., Shyam, R., Sinha, D., Thompson, D.A., and Zacks. D.N. Autophagy in the eye: from physiology to pathophysiology. *Autophagy Rep.* 1: 2178996 (2023)
10. Yamamoto, H., Zhang, S., *Mizushima, N. Autophagy genes in biology and disease. *Nat. Rev. Genet.* 24:382-400 (2023) doi: 10.1038/s41576-022-00562-w
11. *Zhang, S., *Mizushima, N. The autophagy pathway beyond model organisms: an evolutionary perspective. *Autophagy* 19:1-2 (2023)
12. Yim, W.W., *Yamamoto, H., *Mizushima, N. A HaloTag-based reporter processing assay to monitor autophagic flux. *Autophagy* 19:1363-1364 (2023)
13. Sakamaki, J.-i., *Mizushima, N. Conjugation of the ubiquitin family proteins to phospholipids. *Autophagy* 19:1361-1362 (2023)

Department of Genome Informatics

Professor

Yukinori Okada, M.D.,Ph.D.

Assistant Professor

Kyuto Sonehara, M.D.

※The following information is the same as that of the previous year for certain reasons.

Homepage <http://www.sg.med.osaka-u.ac.jp/index.html>

Introduction and Organization

The Department of Genome Informatics was initially established as the second department of Biochemistry in 1975. Since the structural reconstruction of the School of Medicine in 1997, this Department became one of the Departments of Biochemistry and Molecular Biology of the Graduate School of Medicine. This Department has previously been headed by the four professors (Prof. Kazutomo Imahori, Yoshitaka Nagai, Takao Shimizu, and Hiroyuki Mano). Prof. Yukinori Okada had currently organized this Department since 2022. The Department is constituted of one professor, one assistant professor, one JSPS fellow, and one administrative assistant.

Teaching activities

As one of the Departments of Biochemistry and Molecular Biology, our Department is responsible for the basic lecture series of biochemistry for medical students (M0).

To teach basic theory of statistical genetics and bioinformatics skills, our Department had an open seminar named “Statistical Genetics Summer School” (August 26th-28th, online).

Research activities

The Department is developing research activities on

elucidation of disease biology, genomic drug discovery, and personalized medicine through analysis of human omics analysis. The main research activities this year are as follows:

1) Identification of intracranial germ cell tumor susceptibility genes

Intracranial germ cell tumors account for approximately 10% of pediatric brain tumors in Japan and have a higher incidence in East Asians than in European. We performed genome-wide association analysis (GWAS) of intracranial germ cell tumors. We identified that susceptibility gene mutations in the *BAK1* gene region alter enhancer activity and confer risk of developing the disease.

2) Shared genetic background between autoimmune and allergic diseases

Through the analysis of the human genome information of 840,000 individuals in Japanese and European populations, we identified the shared genetic backgrounds between autoimmune and allergic diseases. It was practically possible to classify autoimmune and allergic diseases based solely on genetics. There are novel genetic variants that are shared in both diseases. Genetic risk was enriched in the HLA gene region in autoimmune diseases, while enriched toward the cytokine gene regions in allergic diseases.

3) Elucidation of the severe COVID-19 biology

In the COVID-19 pandemic, the Japan COVID-19 Task Force was established (Representative: Keio University), which collected genomic DNA, RNA, plasma, and clinical information from >6,000 COVID-19-infected Japanese patients. GWAS was conducted in the young severe patients. We identified DOCK2, an immunoregulatory gene, as a responsible gene for COVID-19 severity, based on blood single-cell analysis and a Syrian hamster infection model.

4) Gene expression analysis of COVID-19

We conducted an eQTL analysis to examine the association between blood cell gene expression and individual differences in human genome sequence in 465 COVID-19-infected patients collected by the Corona Control Task Force. We quantified changes in gene expression regulation patterns according to the severity of COVID-19 infection and reported the involvement of neutrophil activation behind the changes by interaction eQTL analysis of gene expression regulation by COVID-19 severity and genomic mutations. The involvement of neutrophil activation was suggested.

5) Best practices for genomic drug discovery

Through international biobank collaboration, we proposed a best practice of genomic drug discovery to search for candidate compounds based on the GWAS results. The combination of three genomic drug discovery methods enables comprehensive search for drug candidates. The method was applied to 13 diseases including asthma, gout, COPD, and venous thromboembolism, and an drug candidate list containing more than 250 compounds was generated. This was an achievement of the methodology to search for therapeutic drug candidates based on disease genetics.

6) Germline and somatic mutation interactions in cancer development

Based on the large-scale GWAS results for various types of cancer, we constructed a polygenic risk score (PRS) that strongly reflects inborn genetic risk of cancer development. Individuals with high PRS develop cancer at a younger age and have fewer

somatic abnormalities. Such characteristics associated with genetic cancer risk constitution were commonly found in several types of cancer.

7) Identification of rheumatoid arthritis risk genes

Through international collaboration, we conducted a large-scale GWAS of ~280,000 individuals comprising five ethnic groups, including Japanese, and the risk variants associated with rheumatoid arthritis were newly identified. A risk score for predicting the development of rheumatoid arthritis was constructed, and the prediction accuracy in the East Asian population was confirmed to be comparable to that in the Europeans.

8) Database of the gut microbiome bacteria and virus of Japanese

We reconstructed bacterial and viral genome sequences from the gut microbiome sequencing of 787 Japanese individuals as a database. The constructed database included bacterial and genetic information related to Japanese food (e.g., nori and natto). Using the gut virus genome database, we conducted an analysis focusing on crAss-like phage. We reported that β crAss-like phage was less common in Asians, Europeans, and Americans, while more common in Africans and Oceanians. CrAss-like phage in multiple subfamilies is decreased in autoimmune diseases.

References

1. Namba S, Saito Y, Kogure Y, Masuda T, Bondy ML, Gharahkhani P, Gockel I, Heider D, Hillmer A, Jankowski J, MacGregor S, Maj C, Melin B, Ostrom QT, Palles C, Schumacher J, Tomlinson I, Whiteman DC, Okada Y, Kataoka K. (2023) Common germline risk variants impact somatic alterations and clinical features across cancers. *Cancer Res* 83:20-27.
2. Tomofuji Y, Kishikawa T, Maeda Y, Ogawa K, Otake-Kasamoto Y, Kawabata S, Nii T, Okuno T, Oguro-Igashira E, Kinoshita M, Takagaki M, Oyama N, Todo K, Yamamoto K, Sonehara K, Yagita M, Hosokawa A, Motooka D, Matsumoto Y, Matsuoka H, Yoshimura M, Ohshima S, Shinzaki S, Nakamura S, Iijima H, Inohara H, Kishima H, Takehara T, Mochizuki H, Takeda K,

- Kumanogoh A, Okada Y. (2022) Prokaryotic and viral genomes recovered from 787 Japanese gut metagenomes revealed microbial features linked to diets, populations, and diseases. *Cell Genom* 2:100219.
3. Ishigaki K, Sakaue S, Terao C, Luo Y, Sonehara K, Yamaguchi K, Amariuta T, Too CL, Laufer VA, Scott IC, Viatte S, Takahashi M, Ohmura K, Murasawa A, Hashimoto M, Ito H, Hammoudeh M, Emadi SA, Masri BK, Halabi H, Badsha H, Uthman IW, Wu X, Lin L, Li T, Plant D, Barton A, Orozco G, Verstappen SMM, Bowes J, MacGregor AJ, Honda S, Koido M, Tomizuka K, Kamatani Y, Tanaka H, Tanaka E, Suzuki A, Maeda Y, Yamamoto K, Miyawaki S, Xie G, Zhang J, Amos CI, Keystone E, Wolbink G, van der Horst-Bruinsma I, Cui J, Liao KP, Carroll RJ, Lee HS, Bang SY, Siminovitch KA, de Vries N, Alfredsson L, Rantapää-Dahlqvist S, Karlson EW, Bae SC, Kimberly RP, Edberg JC, Mariette X, Huizinga T, Dieudé P, Schneider M, Kerick M, Denny JC, BioBank Japan Project, Matsuda K, Matsuo K, Mimori T, Matsuda F, Fujio K, Tanaka Y, Kumanogoh A, Traylor M, Lewis CM, Eyre S, Xu H, Saxena R, Arayssi T, Kochi Y, Ikari K, Harigai M, Gregersen PK, Yamamoto K, Louis Bridges S Jr, Padyukov L, Martin J, Klareskog L, Okada Y, Raychaudhuri S. (2022) Multi-ancestry genome-wide association analyses identify novel genetic mechanisms in rheumatoid arthritis. *Nat Genet* 54:1640-1651.
4. Namba S, Konuma T, Wu KH, Zhou W, Global Biobank Meta-analysis Initiative, Okada Y. (2022) A practical guideline of genomics-driven drug discovery in the era of global biobank meta-analysis. *Cell Genom* 2:100190.
5. The GIANT consortium. (2022) A saturated map of common genetic variants associated with human height. *Nature* 610:704-712.
6. Japan COVID-19 Task Force. (2022) The whole blood transcriptional regulation landscape in 465 COVID-19 infected samples from Japan COVID-19 Task Force. *Nat Commun* 13:4830.
7. Japan COVID-19 Task Force. (2022) DOCK2 is involved in the host genetics and biology of severe COVID-19. *Nature* 609:754-760.
8. COVID-19 Host Genetics Initiative. (2023) A second update on mapping the human genetic architecture of COVID-19. *Nature* 621:E7-E26.
9. Sonehara K, Kimura Y, Nakano Y, Ozawa T, Takahashi M, Suzuki K, Fujii T, Matsushita Y, Tomiyama A, Kishikawa T, Yamamoto K, Naito T, Suzuki T, Yamaguchi S, Miwa T, Sasaki H, Kitagawa M, Ohe N, Fukai J, Ogiwara H, Kawamura A, Miyawaki S, Matsuda F, Kiyokawa N, Ichimura K, Nishikawa R, Okada Y, Terashima K. (2022) A common deletion at BAK1 reduces enhancer activity and confers risk of intracranial germ cell tumors. *Nat Commun* 13:4478.

Department of Physiological Chemistry and Metabolism

Professor

Hiroki Kurihara, M.D., Ph.D.

Associate Professor

Yukiko Kurihara, M.D., Ph.D.

Research Associate

Yasunobu Uchijima, Ph.D.

Project Assistant Professor

Akiyasu Iwase, Ph.D.

Project Researcher

Hiroki Higashiyama, Ph.D.

※The following information is the same as that of the previous year for certain reasons.

Homepage <http://bio.m.u-tokyo.ac.jp/home-j.html>

Introduction and Organization

The Department of Physiological Chemistry and Nutrition, the predecessor of the present department, was founded in 1952. Upon the restructuring of the university system in 1997, the department was renamed 'Department of Physiological Chemistry and Metabolism' as one unit of the Specialty of Molecular Cell Biology. The present members include the above stuffs, 4 graduate students (doctor course) and 1 secretary. Professor Tomoichiro Asano (Hiroshima University) is invited as a part-time lecturer to instruct graduate students and give lectures to undergraduate students.

Teaching activities

We give a series of lectures and laboratory courses on biochemistry and molecular biology for undergraduate students from Faculty of Medicine and Faculty of Science. We also accept undergraduate students taking the MD-researcher developing program,

"Free Quarter" and "Early-Exposure-to-Medicine" courses every year. Several students are staying in our lab beyond the term to join our research.

For graduate students, we hold progress-report meeting and journal club every week, and sometimes invite established scientists for seminar to encourage scientific discussion.

Research activities

Our research is aimed at understanding molecular mechanisms underlying morphogenesis of the cranio-facial and cardiovascular structures.

(1) Craniofacial development

The branchial (pharyngeal) arches are a segmental series of bulging structures common and characteristic for all vertebrate embryos. They are mainly formed by migratory cranial neural crests, which give rise to various skeletal components including the jaw and middle ear structures. We have revealed that endothelin-1 (ET-1), first identified as an endothelium-

derived vasoconstrictor peptide, and its receptor ETAR signaling acts as a molecular switch that determines the lower jaw identity by using mouse genetics.

From this research, several new insights in the field of evolutionary developmental biology have been obtained. In mouse embryos, the absence of the Endothelin signal results in the failure to form the eardrum and the external ear canal. In contrast, in chicken embryos, there is instead an occurrence of duplication formation. This reveals that the eardrum is a product of convergent evolution that independently evolved in mammals and reptiles/birds. Furthermore, the facial structure of mammals deviates significantly from the common facial development pattern found in jawed vertebrates. It undergoes dynamic evolution, altering the tip of the upper jaw in reptiles and amphibians to create a protruding nose while simultaneously developing new bones to reshape the mouth tip. This has been elucidated through experimental embryology and comparative studies, including the analysis of fossils.

Recently, two different recurrent mutations in the Endothelin-A receptor (ETAR) gene *EDNRA* have been identified as causative for mandibulofacial dysostosis with alopecia (MFDA), a rare congenital disorder in humans. The mechanism of its pathogenesis has been elucidated through the use of mouse genetics, pharmacological experiments, and molecular dynamics (MD) simulations. This has revealed that the single amino acid *EDNRA* mutations distant from the ligand binding site allosterically affect ligand binding, inhibiting ligand dissociation and increasing binding affinity.

(2) Cardiac development

We have advanced our analysis regarding three cell types that migrate through the cardiac outflow tract and contribute to heart formation:

- ① We clarified that mesodermal cells from the extraembryonic somatopleure, which serves as the amniotic primordium, migrate into the embryo and differentiate into cardiomyocytes and vascular endothelial cells. We also revealed that BMP and FGF signals are involved in inducing these differentiations.
- ② Through transcriptome analysis of neural crest cells migrating into the heart and spatial

transcriptome analysis, we unveiled a diverse cell population, including undifferentiated cell groups resembling stem cells and precursors, as well as smooth muscle-like cells. We also conducted a time-evolving lineage prediction for these cell populations.

- ③ In coronary artery formation, we found the involvement of lymphatic endothelial cells that are believed to originate from the periaortic capillary plexus around the aortic root during embryonic development. We demonstrated the role of Semaphorin signals in this process.

Furthermore, through comparative anatomical and developmental analysis of coronary arteries, we elucidated that in amphibians, teleost fish, and cartilaginous fish, the primary vessels formed during embryonic development directly supply the heart, whereas, in amniotes (mammals, birds, reptiles), these primary vessels undergo remodeling during development, forming a new entrance to establish the coronary arteries. This provides a new foundation for understanding the causes of congenital coronary artery abnormalities.

(3) Angiogenesis

Angiogenesis is a morphogenetic process that produces branching vascular structures during embryogenesis and various (patho-)physiological conditions. We have identified characteristic cellular behaviors in angiogenic processes, including dynamic changes in forward-backward movement, tip cell overtaking and resultant cell mixing. Although the cellular behaviors appear complex and arbitrary, different types of mathematical modeling (stochastic vs. deterministic) and experimental verification indicated that some deterministic cell-cell interactions are critical for vascular elongation and possibly branching. Recently, we found differences in branch-forming capacity among cell types and some regularities in directional cell movement using in vitro angiogenesis experiments using mouse vascular explants and an endothelial cell line by refined cell-tracking system. Together with single-cell analyses of cell movement and gene expression, novel mathematical modeling and experimental verification using constitutional approaches are under way in collaboration with Professor Tetsuji Tokihiro (Graduate School of

Mathematical Sciences, The University of Tokyo, Musashino University) and his colleagues, to elucidate the possible cellular mechanisms underlying branch formation in angiogenesis.

To elucidate the collective motility characteristics of endothelial cells that enable sprout elongation, we analyzed the dynamics of mouse pancreatic islet microvascular-derived endothelial cell line MS-1 cells. We discovered that their directional movement is influenced by cell contacts, with a combination of linear motion with directionality and rotational movement as its basis. Through various inhibitors and genetic modifications using genome editing, it has become evident that these endothelial cell-specific motility characteristics are specifically regulated by adhesion molecules such as VE-cadherin. Currently, we are advancing the elucidation of the coordination mechanism between cell motility and transcriptional control by contrasting gene expression profiles and cell behavioral phenotypes.

References

1. Aouci R, Soudany ME, Maakoul Z, Fontaine A, Kurihara H, Levi G, Narboux-Nême N. *Dlx5/6* expression levels in mouse GABAergic neurons regulate adult parvalbumin neuronal density and anxiety/compulsive behaviours. *Cells* 11(11): 1739, 2022.
2. Maruyama K, Miyagawa-Tomita S, Haneda Y, Kida M, Matsuzaki F, Imanaka-Yoshida K, Kurihara H. The cardiopharyngeal mesoderm contributes to lymphatic vessel development. *eLife* e81515, 2022.
3. Hayashi T, Yura F, Mada J, Kurihara H, Tokihiro T. Pattern formation of elliptic particles by two-body interactions: A model for dynamics of endothelial cells in angiogenesis. *J. Theor. Biol.* 555:111300, 2022.
4. Higashiyama H, Koyabu D, Kurihara H. Evolution of the therian face through complete loss of the premaxilla. *Evol. Dev.* 25(1):103-118, 2023.
5. Kurihara Y, Ekimoto T, Gordon CT, Uchijima Y, Sugiyama R, Kitazawa T, Iwase A, Kotani R, Asai R, Pingault V, Ikeguchi M, Amiel J, Kurihara H. Mandibulofacial dysostosis with alopecia results from ETAR gain-of-function mutations via allosteric effects on ligand binding. *J. Clin. Invest.* 133(4):e151536, 2023.
6. Shima Y, Sasagawa S, Ota N, Oyama R, Tanaka M, Kubota-Sakashita M, Kawakami H, Kobayashi M, Takubo N, Ozeki AN, Sun X, Kim YJ, Kamatani Y, Matsuda K, Maejima K, Fujita M, Noda K, Kamiyama H, Tanikawa R, Nagane M, Shibahara J, Tanaka T, Rikitake Y, Mataga N, Takahashi S, Kosaki K, Okano H, Furihata T, Nakaki R, Akimitsu N, Wada Y, Ohtsuka T, Kurihara H, Kamiguchi H, Okabe S, Nakafuku M, Kato T, Nakagawa H, Saito N, Nakatomi H. Increased PDGFRB and NF- κ B signaling caused by highly prevalent somatic mutations in intracranial aneurysms. *Sci Transl Med.* 15(700):eabq7721, 2023.
7. Tonami K, Hayashi T, Uchijima Y, Kanai M, Yura F, Mada J, Sugahara K, Kurihara Y, Kominami Y, Ushijima T, Takubo N, Liu X, Tozawa H, Kanai Y, Tokihiro T, Kurihara H. Coordinated linear and rotational movements of endothelial cells compartmentalized by VE-cadherin drive angiogenic sprouting. *iScience.* 26(7):107051, 2023.
8. Oda H, Tonami K, Nakata Y, Takubo N, Kurihara H. Persistent homological cell tracking technology. *Sci Rep.* 13(1):10882, 2023.
9. Mizukami K, Higashiyama H, Arima Y, Ando K, Okada N, Kose K, Yamada S, Takeuchi JK, Koshiba-Takeuchi K, Fukuhara S, Miyagawa-Tomita S, Kurihara H. Coronary artery established through amniote evolution. *eLife* 12:e83005, 2023.
10. Watanabe Y, Wang Y, Tanaka Y, Iwase A, Kawamura T, Saga Y, Yashiro K, Kurihara H, Nakagawa O. Myocardial progenitor cells defined by *Hey2* enhancer activity at the early stage of cardiac crescent formation specifically differentiate into cardiomyocytes of the left ventricle. *Proc. Natl. Acad. Sci. U.S.A.* 120(37): e2307658120, 2023.
11. Liu N, Kawahira N, Nakashima Y, Nakano H, Iwase A, Uchijima Y, Wu SM, Minamisawa S, Kurihara H, Nakano A. Notch and retinoid acid signals regulate macrophage formation from endocardium downstream of *Nkx2-5*. *Nat Commun.* 14(1):5398, 2023.
12. Agostini V, Tessier A, Djaziri N, Khonsari RH,

- Galliani E, Kurihara Y, Honda M, Kurihara H, Hidaka K, Tuncbilek G, Picard A, Konas E, Amiel J, Gordon CT. Biallelic truncating variants in VGLL2 cause syngnathia in humans. *J Med Genet.* jmg-2022-109059, 2023.
13. Sakai K, Hayashi T, Sakai Y, Mada J, Tonami K, Uchijima Y, Kurihara H, Tokihiro T. A three-dimensional model with two-body interactions for endothelial cells in angiogenesis. *Sci Rep.* 13(1): 20549, 2023.
14. Haneda Y, Miyagawa-Tomita S, Uchijima Y, Iwase A, Asai R, Kohro T, Wada Y, Kurihara H. Diverse contribution of amniogenic somatopleural cells to cardiovascular development: with special reference to thyroid vasculature. *Dev. Dyn.* 253: 59-77, 2024.

Molecular Cell Biology

3. Advanced Structural Studies

Department of Advanced Structural Studies

Professor

Radostin Danev, Ph.D.

JSPS fellows

Fabian Eisenstein, Ph.D.

Irwin Selvam, Ph.D.

Homepage <http://danevlab.m.u-tokyo.ac.jp>

Introduction and Organization

Our laboratory was established in 2018 and is supported by grants from the Japan Society for the Promotion of Science (JSPS), and Takeda Science Foundation. We also benefit from indirect support through an instrumentation facility grant from the Japan Agency for Medical Research and Development (AMED). Our team includes Radostin Danev (Professor), Fabian Eisenstein (JSPS fellow), and Irwin Selvam (JSPS fellow).

Teaching activities

We provide training and support for the users of the cryo-electron microscopy (cryo-EM) facility at the Graduate School of Medicine. This includes delivering specialized lectures in cryo-EM courses at the University of Tokyo and other research institutions in Japan and abroad. Additionally, we present introductory lectures on structural biology as part of the following programs:

- 1) MD scientist training program (MDSTP)
- 2) Master student class
- 3) Ph.D. student guidance
- 4) School of Medicine Introductory Lecture

Research activities

Our research focuses on elucidating the structure-function relationships of proteins and

cellular components. By advancing our understanding of the molecular mechanisms underlying chronic diseases, we aim to contribute to fundamental scientific knowledge and support the development of effective treatments.

Over the past few years, we have been investigating a crucial class of membrane proteins known as G protein-coupled receptors (GPCRs). GPCRs represent the largest family of membrane proteins in the human genome, responsible for sensing and transducing many extracellular signals that regulate various physiological processes. Due to their broad regulatory functions, GPCRs are implicated in numerous chronic diseases such as diabetes, obesity, nervous system disorders, migraines, asthma, allergies, cardiovascular disorders, cancer, and more. Consequently, they constitute the largest group of drug targets and are the subject of more than 30% of approved drugs.

To unravel the mechanisms of GPCR activation and signal transduction at the atomic level, we employ cryo-EM single-particle analysis, a powerful and increasingly prolific technique. In collaboration with a research group at Monash University specializing in GPCR pharmacology, we have studied receptor activation by both native and synthetic ligands. This collaboration has yielded over 40 sub-3 Å unmodified full-length GPCR structures, with approximately half achieving resolutions better than 2.5 Å. This achievement is unprecedented in structural biology,

both in terms of the number of structures resolved and their resolution.

Our success stems from a rigorous and systematic optimization of cryo-EM experimental parameters, including sample preparation and data collection. By combining data collection with iterative testing of experimental factors, we achieved high efficiency without requiring additional time on the costly and heavily booked electron cryo-microscopes. This methodological refinement enabled us to routinely achieve sub-2.5 Å resolution in our recent studies, culminating in the first sub-2 Å resolution reconstructions of GPCR complexes - an accomplishment that remains unsurpassed.

Despite the rapid advances in cryo-EM, many challenges remain. To address these, we are actively developing new experimental methods. One such project involved the FADE (Fast and Accurate Defocus Modulation) method, which introduces real-time synchronous modulation of the electron beam to transform the cryo-EM system into a dynamic, adaptable optical platform. We have successfully built and installed the first FADE prototype on a JEOL JEM-F200 microscope, with hardware performance meeting expectations. Current efforts focus on adapting data processing software to handle FADE-generated datasets. In the near future, this system will be implemented on the JEOL CryoARM 200 microscope at the University of Tokyo, allowing us to demonstrate its capabilities at a higher level.

Other areas of our research include cryo-electron tomography (cryo-ET) of cellular samples combined with advanced sample preparation through cryogenic focused ion beam milling (cryo-FIB). By enabling in situ visualization of proteins and complexes within their native cellular environments, cryo-ET holds immense promise for biological, pharmacological, and medical research. In 2022, we introduced PACE-tomo (Parallel Cryo Electron Tomography), a novel high-throughput approach that significantly accelerates cryo-ET data acquisition by eliminating delays caused by mechanical stage movements. PACE-tomo increases data throughput fivefold, paving the way for breakthroughs in the field and advancing toward the ambitious goal of “visual proteomics,” where individual proteins and their interactions can be mapped within cellular volumes.

We are also expanding our investigations toward state-of-the-art deep learning (DL) experiment automation for both cryo-EM single particle analysis and cryo-electron tomography. DL methods have become ubiquitous in many research areas, and some groups are already developing DL-based experimental frameworks for cryo-EM and cryo-ET. However, many experimental steps still require human intervention. Most of these actions involve image evaluation and feature recognition, making them perfect candidates for DL algorithms, which have already been proven to match or surpass human performance in such activities. With further automation, experiments will become more efficient, allowing researchers to operate microscopes remotely while working on other important tasks. The quality and quantity of data will improve, thereby increasing the level and number of scientific results.

References

1. Eisenstein F, Yanagisawa H, Kashihara H, Kikkawa M, Tsukita S, **Danev R**. Parallel cryo electron tomography on in situ lamellae. *Nat Methods*. 2023;20(1):131-138.
2. Vuckovic Z, Wang J, Pham V, Mobbs JI, Belousoff MJ, Bhattarai A, Burger WAC, Thompson G, Yeasmin M, Nawaratne V, Leach K, van der Westhuizen ET, Khajehali E, Liang YL, Glukhova A, Wootten D, Lindsley CW, Tobin A, Sexton P, **Danev R**, Valant C, Miao Y, Christopoulos A, Thal DM. Pharmacological hallmarks of allostery at the M4 muscarinic receptor elucidated through structure and dynamics. *Elife*. 2023;12:e83477.
3. Burger WAC, Pham V, Vuckovic Z, Powers AS, Mobbs JI, Laloudakis Y, Glukhova A, Wootten D, Tobin AB, Sexton PM, Paul SM, Felder CC, **Danev R**, Dror RO, Christopoulos A, Valant C, Thal DM. Xanomeline displays concomitant orthosteric and allosteric binding modes at the M4 mAChR. *Nat Commun*. 2023;14(1):5440.
4. **Danev R**, 吉川 雅英 「電子線トモグラフィー」, In: クライオ電子顕微鏡ハンドブック, 難波 啓一 (著, 監修), 加藤 貴之 (著, 監修), 牧野 文信 (著, 監修), NTS inc. 2023.

Functional Biology

1. Physiology

Department of Integrative Physiology

Professor

Kenichi Ohki, M.D., Ph.D.

※The following information is the same as that of the previous year for certain reasons.

Homepage <https://physiol1.m.u-tokyo.ac.jp/ern24596/en/>

Introduction and Organization

This laboratory was initially established in 1877 as The First Department of Physiology, and reorganized in 1997 as Laboratory of Integrative Physiology in the Department of Physiology. Our laboratory cooperates with other laboratories in the Department of Physiology, that is, Laboratory of Molecular/Cellular Physiology and Laboratory of Neurophysiology, in teaching activities for undergraduate courses and the nursing school. The fields in which our laboratory specializes span the entire spectrum of *animal functions* of physiology, including general physiology, sensory physiology, endocrinology, neurophysiology, higher nervous functions and cognitive neurosciences.

Education

The staff members as well as experts from other universities take part in giving lectures and laboratory courses to the undergraduate students of the Medical School. The lectures are aimed at providing a clear understanding of the hierarchical functional organizations of living systems. The curriculum is updated every year. For example, a new electrocardiogram experiment in humans was introduced to the laboratory course, in which students learned human physiology of electrocardiogram, its practical procedure in clinical settings and its cellular physiological origins. This practice gained popularity and interest among students. We accept *Free-Quarter* students every year. Usually these students' activities are not limited to one *Quarter*. Some of these students

completed their own projects, and gave oral presentations in international meetings and published original papers in top-rank international journals. It is not rare that students who enjoyed his/her *Free-Quarter* decided to get into the Ph.D. course after the completion of the 2-year clinical training and started to study neurophysiology in our laboratory. Furthermore, we accepted a Ph.D.-M.D course student who enjoyed his *Free-Quarter* and decided to get into the Ph.D.-M.D course. Thus the *Free-Quarter* system has proved to provide an excellent basis for bringing up M.D. researchers for future Japanese basic medicine.

To facilitate communication among research groups in our laboratory, a weekly conference is held for discussing current research activities. We also have a monthly joint seminar with Department of Pharmacology. As a part of teaching activity for the graduate students, we have another weekly seminar, in which the graduate students learn how to give presentations and hold discussions and debates.

Research

Most of our research is focused on the higher brain function of the mammalian central nervous system.

(1) Hierarchical and parallel visual networks in the cerebral cortex are conserved across mammalian species and are considered the basic structure of visual information processing in the brain. During development, the brain forms the complex visual

network based on both gene expression and neural activity including spontaneous activity. The development of neural networks is an important topic in the neuroscience. However, previous investigations have been limited to lower order pathways from the periphery to the primary sensory cortex via the thalamic nuclei. Thus, the development of the entire neural network, including higher order cortical areas and higher-order thalamic nuclei, remains largely unexplored.

To elucidate the development of neural networks, it is necessary to investigate the formation of inter-areal connections throughout the visual network, including cortical and thalamic visual areas. However, it has been technically difficult to precisely identify the locations of the visual areas in the immature, developing brain. We found that the locations of the primary (V1) and higher visual areas can be identified by analyzing spontaneous activity observed in the developing mouse cortex. Using this method, we investigated how interregional connections were formed throughout the mouse visual network. In addition, we examined the functional role of spontaneous activity in the formation of intercortical connections.

We found that early in development, the projections from the thalamic nuclei to the visual cortex (primary thalamic nuclei to V1 and higher thalamic nuclei to higher visual cortex) were established before the formation of the intercortical connections. In addition, the primary and higher thalamic nuclei each received input from the retina through independent pathways, forming parallel pathways from the retina to V1 or higher visual cortex.

Functional calcium imaging of neuronal activity revealed that, spontaneous activity propagated from the retina to the cortex through the parallel pathways, and that the activity showed retinotopic patterns in both the thalamic nuclei and visual cortical areas including V1 and higher visual areas. These results indicate that these parallel pathways have retinotopic connections even at an early stage of development and suggest that the parallel pathways may support the formation of intercortical connections based on their retinotopic structures.

To investigate the role of spontaneous retinal activity in the formation of inter-cortical connections, we

removed the retinal activity immediately after birth. Removal of the retinal activity disrupted the projection from V1 to higher visual areas, indicating that spontaneous retinal activity is important for the formation of intercortical connections.

This study not only demonstrates the developmental process of the cortical neural network, but also provides a basic knowledge for elucidating the mechanisms underlying the neural network formation depending on neural activity and gene expression.

(2) In adult mice, a higher order thalamic nucleus sends its axons not only to higher visual areas, but also to the primary visual cortex (V1). However, the function of the latter pathway has not been fully understood. Using functional axon imaging, we revealed that the higher order thalamic nucleus sends different visual information to V1 compared to the primary thalamic nucleus, indicating the different roles of the primary and higher thalamic nuclei in modulation of V1 activity.

(3) Neural activity is important for the development of projections of interhemispheric callosal connections. However, when the neural activity is important during the development of the callosal projections has not been investigated. We genetically controlled the activity of the callosal projections and showed that the neural activity during a limited developmental period is important for the proper formation of the callosal projections, suggesting a critical period for neural activity dependence in the development of the callosal connections.

Publications

- (1) Tomonari Murakami, Teppei Matsui, Masato Uemura, Kenichi Ohki. Modular strategy for development of the hierarchical visual network in mice *Nature*, 608, 578-585, 2022
- (2) Satoru Kondo, Yuko Kiyohara, Kenichi Ohki. Response Selectivity of the Lateral Posterior Nucleus Axons Projecting to the Mouse Primary Visual Cortex *Frontiers in neural circuits* 16: 825735, 1-13, 2022;

- (3) Yuto Tezuka, Kenta M Hagihara, Kenichi Ohki, Tomoo Hirano, Yoshiaki Tagawa. Developmental stage-specific spontaneous activity contributes to callosal axon projections *Elife* 11, e72435, 2022

Department of Cellular and Molecular Physiology

Professor

Masanori Matsuzaki, Ph.D.

Lecturer

Teppei Ebina, Ph.D.

Research Associate

Shin-Ichiro Terada, Ph.D.

Masashi Kondo, Ph.D.

※The following information is the same as that of the previous year for certain reasons.

Homepage <http://plaza.umin.ac.jp/~Matsuzaki-Lab/>

Introduction and Organization

The Department of Cellular and Molecular Physiology succeeded the former ‘Second Department of Physiology’, and belongs to the Department of Physiology. We participate in the teaching of physiology at undergraduate school and graduate school.

The present members include the above staff, 2 secretary staff, 4 technical staff, 1 project research associate, 6 graduate students.

Teaching activities

The department provides lectures and practice in physiology for undergraduate students. We teach imaging, computational neuroscience, and cellular and molecular physiology methods for free quarter students. The department provides also lectures and instructions for laboratory research for graduate and undergraduate students in the fields of neurophysiology and molecular and cellular imaging. Seminars, progress reports, and journal club for graduate students are routinely provided. Monthly joint seminars (Functional Biology Seminars) are also provided for graduate students.

Research activities

Various firing patterns of many cortical neurons represent information processing in the brain. The microarchitecture of synaptic connections control information processing in cortical circuits. The structure and location of synapses determine and modify the strength of this information processing. The aim of our laboratory is to reveal how information is formed, maintained, selected, and decoded in the brain at the levels of single cells and of single synapses. To do so, we mainly use two-photon microscopy that allows us to see fluorescence signals from deep within living tissue, developing novel photostimulation methods and animal behavioral tasks. The goals of our recent studies are to reveal how voluntary movement is memorized and represented in cortical circuits. In addition, we are working to apply two-photon microscopy to a non-human primate, the common marmoset, in order to understand information processing in the brain, which is relevant to high cognitive functions.

(1) Transition of distinct context-dependent ensembles from secondary to primary motor cortex in skilled motor performance

In practicing short-distance running, one may start running on their own timing or start running in response to the sound of a pistol. The various actions we perform daily can be divided into 'internally generated' movements, which start spontaneously, and 'externally triggered' movements, which start in response to sensory stimuli such as visual and auditory stimuli.

In patients with Parkinson's disease, it is known that while it is difficult to start movements spontaneously, they can relatively robustly initiate movements in response to exogenous stimuli. It is assumed that the neural processing pathways in the brain for these two types of movements are largely different. Previous studies reported that while the higher motor cortex shows neural activity dependent on each start signal, the primary motor cortex exhibits the same activity regardless of the signal. However, it was still unclear what information is transmitted between these areas, how these different activities converge into the same activity, and whether these are dependent on the individual's learning status.

In this study, we first constructed internally generated and externally triggered movement tasks in mice. In these tasks, mice could obtain rewards by pulling a lever either spontaneously or in response to an auditory cue. Next, we investigated the involvement of the higher motor cortex (M2) and primary motor cortex (M1) in these tasks after training the mice, by inhibiting neural activity pharmacologically and optogenetically. When we consistently suppressed activity in both M2 and M1, the success rate decreased regardless of whether the movement was internally generated or externally triggered. However, when suppression was transient after movement initiation, only inhibition of M1 caused motor dysfunction. These results suggest that both M2 and M1 are necessary for task execution, but after movement initiation, the motor execution function shifts to M1, indicating that these two areas may be hierarchically processing information.

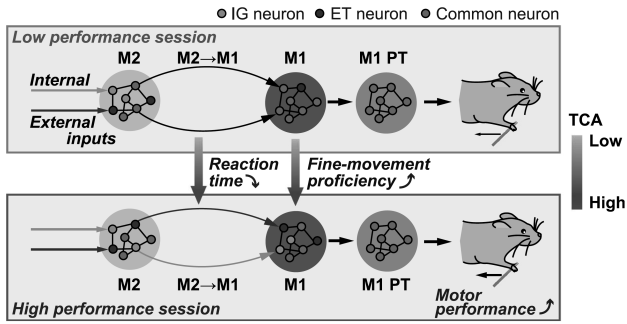
Next, to understand what information is represented in neural activity, we conducted calcium imaging with two-photon microscopy. To clarify how

M2 and M1 interact, it is important to simultaneously measure neural activity in both areas. Our laboratory previously developed microscopy called the 'wide-field two-photon microscopy', which allows sequential measurement of neural activity in separate areas at single-cell resolution using a custom-developed miniaturized optical element. In this study, we further improved this microscopy, nearly doubling the image acquisition speed from about 6 frames per second to approximately 10 frames per second, enabling the capture of more detailed activity changes.

Using this microscopy to examine the activities in the superficial layers of M2 and M1, we confirmed the presence of neural activities responding to the differences in start signals between internally generated and externally triggered movements. To further investigate the information transmitted between areas, we also imaged axons projecting from the thalamus, located beneath the cerebral cortex, to M2, from M2 to M1, and corticospinal tract neurons in the deep layer of M1, conducting comprehensive measurements from M2 input to M1 output. Using machine learning-based decoding analysis, we quantified the context dependency, i.e., whether the movement initiation was internally generated or externally triggered, at the group level for each structure. As a result, while the superficial layer of M2 always showed high context dependency, and the corticospinal tract neurons in M1 always showed low context dependency, the context dependency of axons projecting from M2 to M1 and neurons in the superficial layer of M1 varied significantly between days and animals. Further analysis revealed that the higher the context dependency in both structures, the better the task performance, such as success rate and response time to the sound cue. Additionally, the higher the context dependency in the superficial layer of M1, the better the motor proficiency, such as lever-pulling speed, duration, and reproducibility of lever trajectory.

At the individual cell level, when motor proficiency was high, the number of cells in the superficial layer of M1 with both high context information and high motor information increased, suggesting that the increase in context dependency and motor proficiency at the group level was

interconnected. Even when this reorganization of activity occurred in the superficial layer of M1, there were no significant differences in information representation at the group or individual cell levels in the superficial layer of M2. It is considered that high motor function was realized by reorganizing cell groups that generate motor commands specialized for each context downstream (see Figure below).



The finding in this study that the relationship between the reorganization of context-dependent neural activity and motor proficiency varies greatly depending on the region and layer within the frontal cortex, and that the neural network between context input and motor output dynamically changes, demonstrates the highly adaptive information processing ability of the cerebral cortex. Further research may contribute to the development of high-performance artificial intelligence algorithms that mimic the brain. Additionally, elucidating the mechanisms of internally generated and externally triggered movements is important for understanding Parkinson's disease and holds promise for the development of new treatments.

(2) Development of a bleed-free multi-site automated injection robot for accurate, fast, and dense viral delivery to mouse and marmoset brains

Minimizing invasiveness to the living body is an undoubtedly important issue in biomedical science. Robotics provide one answer to this challenge: automation, and it is awaited especially in the neuroscience and neurosurgical fields, since a brain is one of the most delicate and three-dimensionally complex organs. In the preceding automations, such as craniotomy, patch-clamping, and electrode implantation, are mainly focused on precision of robotic manipulation, which could reduce tissue damage by limiting unexpected movement of surgeons.

However, surgical planning is mostly decided by human, and its automation is still in its infancy.

Here, we developed ARViS: an Automated Robotic Virus injection System. An infrared sensor was used to accurately scan the three-dimensional brain surface with the skull removed. Based on the scanning data, we applied a neural network for retinal vessel segmentation to extract the brain vasculature structure, which were recognized up to 14 μm with 100% accuracy, and optimized the locations of more than 100 injection sites without hitting any blood vessels by developing an original algorithm. Then, a commercially accessible 6-DOF robot precisely moved the needle to each injection site and inserted it to the specified depth. The injection site could be placed as close as 60 μm from vessels and the actual injection depth could only deviate by about $\pm 50 \mu\text{m}$ from the target. Furthermore, because the soft tissue changes shape during needle insertion and because blood vessels run vertically in the brain, the needle angle was aligned perpendicular to the surface, which also contributed to improved accuracy and reduced invasiveness.

As a proof-of-concept experiment, adeno-associated virus (AAV) expressing a Ca^{2+} indicator was injected into over 120 sites of the whole dorsal cerebral cortex of mouse and 266 sites of common marmoset. The risk of major bleeding was only 0.73% in mice (2333 sites) and none was observed in marmoset (266 sites). It took only approximately 20 seconds to change the needle position and angle from one target to another. We clearly detected uniform fluorescence expression over the broad areas of $8 \times 8 \text{ mm}^2$ in the mouse, which covers from the prefrontal to visual cortex in both hemisphere, and $8 \times 14 \text{ mm}^2$ in the marmoset, ranging from area PE to A8. Furthermore, in the mouse, in vivo Ca^{2+} signals from more than 10,000 neurons were simultaneously recorded under an epifluorescence microscope. Thus, ARViS enables bleed-free multi-site automated injection for accurate, fast, and dense virus delivery.

This research provides a new solution for micron-order control of minimally invasive needle insertion into delicate three-dimensional structures avoiding high-risk areas on the surface. It paves the way to the ultra-minimal invasive drug delivery or biopsy targeting at sub-milli order cell aggregation in

the future by combining the existing imaging technology such as MRI or CT, which can be applied to a wide range of clinical medicine, from early detection of breast cancer through biopsies of very small tumors to gene therapy by injecting viral vectors.

(From an abstract in the BIO UT 2022)

References

1. Terada S., Kobayashi K., and Matsuzaki M. Transition of distinct context-dependent ensembles from secondary to primary motor cortex in skilled motor performance. *Cell Reports* 41, 111494, 2022.
2. Terada S., and Matsuzaki M. (News and Views) Silent microscopy to explore a brain that hears butterflies' wings. *Light: Science & Applications* 11, 140, 2022.

Department of Neurophysiology

Professor

Masanobu Kano, M.D., Ph.D.

Research Associate

Takaki Watanabe, Ph.D.

Research Associate

Kazuto Sakoori, Ph.D.

※The following information is the same as that of the previous year for certain reasons.

Homepage <http://plaza.umin.ac.jp/~neurophy/>

Introduction and Organization

This laboratory was founded in 1953 as Department of Neurophysiology, Institute for Brain Research. In 1996, it was integrated into Graduate School of Medicine. The current members of this laboratory are 4 faculty members (professor, lecturer, 2 research associate), 1 postdoctoral fellow, 7 graduate students, and 5 technicians. We teach neurophysiology for medical undergraduates and students in the Master and Ph.D. courses. Our research aims at elucidating cellular and molecular mechanisms underlying the regulation of synaptic transmission and postnatal development of neuronal circuits.

Teaching activities

We teach neurophysiology to medical undergraduates in lectures and practical courses. Lectures are designed for students to learn basic mechanisms underlying the generation of electrical signals, synaptic transmission and their regulations in the nervous system, and roles of the spinal cord, brain stem, and cerebellum in sensorimotor functions. Students also learn how functional neural circuits in the brain are formed and matured during postnatal development. In the practical courses, students perform two types of classical neurophysiology experiments. First, students make intracellular

recordings from frog skeletal muscle fibers and examine the endplate potential for understanding the basic properties of synaptic transmission. Second, students record an electromyogram (EMG) from human gastrocnemius muscles and learn how the stretch reflex works.

We accept Free-Quarter students. Students are encouraged to experience patch-clamp recordings from neurons either in brain slices or in dissociated cultures, or to experience recordings of neuronal activities from living animals.

For the training of Master and Ph.D. course students, we have a weekly conference to discuss current research activities. A laboratory member summarizes his/her recent experimental data or presents papers closely related to his/her research.

Research activities

The brain consists of neuronal circuits in which neurons are connected through numerous synapses. To understand brain function, it is necessary to elucidate mechanisms of synaptic transmission and those underlying changes in synapses related to development, learning, and memory (synaptic plasticity). We take various methodological approaches including electrophysiology, pharmacology, morphology, and genetic engineering of mice. We particularly focus on observing neuronal

activities in real-time in intact neurons. We use whole-cell patch clamp recording, calcium imaging, and two-photon imaging and their combinations in various preparations (cultured neurons, brain slices, and intact animals) and investigate molecular mechanisms of synaptic transmission and plasticity.

The main subjects of our research are as follows

(1) Refinement of synaptic organization during cerebellar development:

In early postnatal days, all Purkinje cells in the cerebellum are innervated by multiple climbing fibers. These surplus climbing fibers are eliminated eventually with the progress of postnatal development, and most Purkinje cells become innervated by single climbing fibers by the end of the third postnatal week in mice. We investigate the mechanisms of how single climbing fibers are selected and how the surplus climbing fibers are eliminated.

(2) Retrograde synaptic modulation mediated by endogenous cannabinoids:

We reported in 2001 that endogenous cannabinoids are released from postsynaptic neurons in an activity-dependent manner, act retrogradely onto presynaptic cannabinoid receptors, and suppress transmitter release. Since then, we have been investigating the mechanisms of this retrograde modulation. We are also interested in elucidating the physiological significance of this phenomenon including learning and memory, addiction, and anxiety.

(3) Neural Activity and its function in intact animals:

To understand the representation of information by specific neurons and their functions *in vivo*, we record and regulate neural activity in intact animals during behavioral tasks by using two-photon microscopy, miniaturized microscopy, and optogenetics. Alongside these, we are also developing various techniques to facilitate these *in vivo* experiments.

formation of columnar axonal projection in the mouse cerebral cortex. *Proc Natl Acad Sci USA*. 2022 Sep 13;119(37):e2122700119. doi: 10.1073/pnas.2122700119. Epub 2022 Sep 6.

- (2) Harbers M, Nakao H, Watanabe T, Matsuyama K, Tohyama S, Nakao K, Kishimoto Y, Kano M, Aiba A. mGluR5 is substitutable for mGluR1 in cerebellar Purkinje cells for motor coordination, developmental synapse elimination, and motor learning. *Cells*. 2022 Jun 23;11(13):2004. doi: 10.3390/cells11132004.
- (3) Sakamoto M, Inoue M, Takeuchi A, Kobari S, Yokoyama T, Horigane SI, Takemoto-Kimura S, Abe M, Sakimura K, Kano M, Kitamura K, Fujii H, Bito H. A Flp-dependent G-CaMP9a transgenic mouse for neuronal imaging in vivo. *Cell Rep Methods*. 2022 Feb 14;2(2):100168. doi: 10.1016/j.crmeth.2022.100168. eCollection 2022 Feb 28.
- (4) Sugaya Y, Kano M. Endocannabinoid-mediated control of neural circuit excitability and epileptic seizures. *Front Neural Circuits*. 2022 Jan 3;15:781113. doi: 10.3389/fncir.2021.781113. eCollection 2021.

References

- (1) Itami C, Uesaka N, Huang JY, Lu HC, Sakimura K, Kano M, Kimura F. Endocannabinoid-dependent

Functional Biology

2. Pharmacology

Department of Cellular and Molecular Pharmacology

Professor

Kenzo Hirose, M.D., Ph.D.

Lecturer

Shigeyuki Namiki, Ph. D., Daisuke Asanuma, Ph. D.

Assistant Professor

Hirokazu Sakamoto, Ph. D.

※The following information is the same as that of the previous year for certain reasons.

Homepage <http://www.pharmacol.m.u-tokyo.ac.jp>

Introduction and Organization

Our department was founded in 1885 and collaborates with the Department of Systems Pharmacology in the education of undergraduate medical students.

Teaching activities

Pharmacology lectures and laboratory courses for the medical students are given by the staff members of both Departments of Pharmacology. We also invite seven outside expert lecturers to cover rapidly developing fields in pharmacology and related medical sciences. The laboratory courses include both traditional and advanced pharmacological experiments. A new intensive laboratory course for medical students started in the year 2001, and we participated in the program. We also give lectures for graduate students including master course students and Ph.D. candidates.

Research activities

A goal of our research is to elucidate regulation mechanisms of cell function through the development of novel technologies. The main subjects of our

research are as follows.

1) Development of high-performance fluorescence probes for visualizing neurotransmitters

Imaging techniques which visualize neurotransmitters in living neurons are powerful methods to understand the mechanism underlying synaptic transmission in neuronal circuits. To facilitate this process, we developed a high-throughput screening system based on 96-well plate format protocol. After screening, we obtained high-performance glutamate probes showing large fluorescence changes upon glutamate binding. This result indicates that our screening system should be applicable to develop fluorescence probes for signaling molecules other than glutamate in short periods.

2) Study of the mechanism underlying the exocytosis of neurotransmitter

For understanding of regulation mechanism underlying neuronal circuit in mammalian central nervous system, elucidation of the neurotransmitter release machinery is indispensable. Aiming at imaging neurotransmitter glutamate, we developed a novel optical glutamate probe by our high-throughput screening system as described above. Using this probe,

we successfully visualized presynaptically released glutamate with a single synapse resolution in cultured hippocampal neurons. We quantitatively analyzed released glutamate at individual synapses and revealed that single hippocampal synapses contain several release units. Furthermore, we have succeeded in imaging spatiotemporal dynamics of glutamate in the extrasynaptic space in brain slices and *in vivo*. This study demonstrated that bursting synaptic activities cause glutamate spillover from the synaptic cleft to activate perisynaptic metabotropic glutamate receptors, and will provide a basis for the research of extrasynaptic glutamate transmission that is involved in many important brain functions. These results indicate that our glutamate probe is useful to directly assess synaptic functions including presynaptic modulation and plasticity.

3) Analysis of supra-molecular assemblies of synaptic molecules in central synapse

Recently, nanoscale molecular distribution in synapses is suggested to be a key determinant of synaptic function. To reveal the relationship between the nanoscale molecular assemblies and synaptic functions, we are trying to perform a super resolution microscopic analysis in combination with glutamate imaging. These advanced imaging techniques revealed that dynamics of neurotransmitter release is precisely controlled by the highly coordinated nanoscale molecular assemblies of presynaptic molecules. We are also trying to identify the functional changes in nanoscale molecular assemblies in psychiatric disease model.

References

1. Miyano, R., Sakamoto, H., Hirose, K., & Sakaba, T. (2022). RIM-BP2 regulates Ca^{2+} channel clustering and neurotransmitter release at hippocampal mossy fiber terminals. *bioRxiv*, 2022-08.
2. Sakamoto, H., Kimpara, N., Namiki, S., Hamada, S., Ohtsuka, T., & Hirose, K. (2022). Synapse type-specific molecular nanoconfigurations of the presynaptic active zone in the hippocampus identified by systematic nanoscopy. *bioRxiv*, 2022-03.

Department of Systems Pharmacology

Professor

Hiroki R. Ueda, M.D., Ph.D.

Project Associate Professor

Yoichi Minami, Ph.D.

Full-time Lecturer

Koji L. Ode, Ph.D.

Katsuhiko Matsumoto, Ph.D.

Project Lecturer

Akifumi Kishi, Ph.D.

Research Associate

Daisuke Tone, Ph.D.

Project Research Associate

Yasuhiro Tomita, M.D., Ph.D.

Homepage <https://sys-pharm.m.u-tokyo.ac.jp/>

Teaching activities

Our department, in collaboration with the department of cellular and molecular pharmacology, takes responsibility for lectures and laboratory courses on pharmacology for the undergraduate students of the faculty. There are 39 lectures per year including those given by seven invited lectures to cover specialized and currently highlighted fields in pharmacology. We offer several laboratory courses, and all the members of the department participate in the courses to provide close consultation for the students.

For the graduate students, there are series of seminars on physiology and neuroscience. We also have research seminars to discuss and stimulate the research activities of the graduate students in the department.

Research activities

Department of systems pharmacology is conducting research to establish organism-level systems biology and pharmacology using sleep-wake cycle as a model system, which is common to organisms with a central nervous system and one of the main factors that dictate the dynamics of social behavior. With our members from different backgrounds, we would like to realize systems biology at the organism level including human, leading to greater understanding and even control of organismal pathophysiology. To this end, we specifically focus on the cellular circuits controlling the sleep/wake cycle and address the hourglass mechanism of sleep, a homeostatic- and circadian-dependent regulation of sleep amount and timing. We are also planning on multi-scale research activities covering a series of length scales; molecule-to-cell, cell-to-tissue, and tissue-to-organism

to envision such complicated underlying mechanism. We have been devoting our research to two technological challenges; 1) next-generation mammalian reverse genetics, where we can produce genetically modified mice in a high-throughput fashion, 2) system-level identification and analysis of cellular circuits in the whole-organ (especially, the whole-brain) and whole-body, where we can identify individual cells or cellular circuits in the whole-organ and whole-body. Combined with these techniques, we investigate how the average (diurnality or nocturnality), the dispersion (the length of sleeping time), and the amount (insomniac or hypersomniac responses) of sleep during circadian time are determined by environments and history of activities. In addition, we are developing human sleep analysis techniques using wearable devices, and aim to realize a series of human sleep studies that incorporate large-scale human sleep phenotyping, genomic analysis, and proof of causality using animal models.

1) Next-generation mammalian reverse genetics

In the conventional method for production of genetically-modified mice, a single line of gene-targeted ES cells is injected into host embryos (typically use blastocysts) to generate chimera mice comprising a mixture of ES- and host-derived cells. In addition, multiple mating procedures are needed to generate the desired genetically modified mouse strain, which typically takes from 9 months to several years. Such multiple rounds of mating procedures are necessary to produce gene knockout / knock-in mice in the conventional method, which was usually a bottleneck to promote organism-level system biology. Therefore, we propose the concept of "next-generation mouse genetics" which creates genetically modified mice without mating and uses it for analysis. We implemented the concept by developing the triple-CRISPR method (Sunagawa et al., Cell Rep. 2016) and the ~100% ES cell-derived mice (ES mice) production method (Ode et al., Mol. Cell 2017; Ukai et al. Nat Protoc. 2017).

2) System-level identification and analysis of cellular circuits in the whole-organ and whole-body

The comprehensive identification of molecular circuits at the organism level also requires accurate

(>90%) phenotype analysis. In neuroscience, sleep/wake behavior is an intriguing phenotype, because sleep disorders (e.g., insomnia or hypersomnia) are sensitive and informative symptoms of almost all psychological disorders. Sleep/wake states have been characterized in humans by electroencephalography (EEG) and electromyography (EMG). Characteristic EEG/EMG patterns during sleep and waking are preserved in mammals and can be measured by electrodes surgically implanted in the brain and muscles. However, such recording requires special surgical skills, and the surgery is highly invasive, requiring a long recovery period (more than 10 days) after implantation before sleep/wake recording. Furthermore, the EEG/EMG data are often manually annotated and classified into sleep/wake phenotypes by visual assessment, which can be time consuming and somewhat subjective. To develop a scalable, non-invasive, fully automated sleep/wake recording method for comprehensive studies, we have developed 1) an automated EEG/EMG analysis software (FASTER, Sunagawa et al., Genes Cell 2013; FASTER2, Yamada et al., Eur. J. Neurosci., 2024), 2) a respiration-based, non-invasive, fully automated system (SSS) (Sunagawa et al., Cell Rep. 2016).

To highlight the regulatory cellular networks in the sleep/wake rhythm, we facilitate identifying sleep/wake regulating cells in the whole-brain in a comprehensive and parallelized manner. CUBIC (Clear, Unobstructed Brain/Body Imaging Cocktails and Computational Analysis) is a great leap forward. It offers a simple tissue clearing protocol by using aminoalcohols and an unprecedented rapid whole-brain and whole-body imaging at single-cell resolution (represented by Susaki et al., Cell, 2014; Tainaka et al., Cell 2014; Tainaka et al., Cell Rep. 2018; Murakami et al., Nat. Neurosci. 2018). The development of the CUBIC method has evolved into the development of microscopes for high-speed imaging (Matsumoto et al., Nat. Protoc. 2019), the extension of technology for immunostaining of three-dimensional tissues (Susaki et al., Nat. Commun. 2020), and the development of a data analysis platform for whole-brain single-cell analysis (Mano et al., Cell Rep. Methods 2021). We have also published results of the application of CUBIC to organs other than the brain, including the proposal of the concept

of "cellomics" (Mitani et al., Nat. Methods, 2024) and the establishment of a high-throughput transparency, staining, and analysis pipeline for mouse organs (Akiyama et al., Nat. Protoc., 2024).

3) Mechanism of dynamic homeostasis in sleep/wake cycle: phosphorylation hypothesis of sleep

Sleep amount during a day is under homeostatic control, in which sleep pressure accumulates during awake time and gradually decreases during sleep. Sleep deprivation further promotes the accumulation of sleep pressure, resulting in the longer/deeper sleep in the next cycle. The required sleep duration in a day is mostly determined genetically as evident from the fact that each animal species shows characteristic different sleep duration. However, detailed molecular mechanisms underlying the control of sleep duration in mammals are still elusive. Using triple-target CRISPR, SSS, and CUBIC techniques together with a computational model that simulates the membrane potential of cortex neuron regulated by a group of ion channels, we have discovered and proposed that Ca^{2+} -dependent neuronal hyperpolarization pathway affects sleep duration in mammals (Sunagawa et al., Cell Reports 2016; Tatsuki et al., Neuron 2016; Yoshida et al. PNAS 2019; Yamada et al., iScience 2022).

We have further been investigating molecules that regulate the transition and consolidation of sleep and awake phases. In this regard, we have reported a phenotype of *Chrm1* and *Chrm3* double-knockout mice produced by triple-CRISPR technology, which showed a complete loss of REM sleep (Niwa et al., Cell Rep. 2018; Yamada and Ueda, Front. Neurosci. 2020). These results were the first report of essential genes of REM sleep. This study also indicated that REM sleep, defined through EEG-EMG recordings, is not critical for the survival of animals.

In the process of investigating the relationship between Ca^{2+} -dependent regulation of neuronal activity and sleep, we discovered CaMKII α/β as the first sleep-inducing protein kinase in mammals (Tatsuki et al., Neuron 2016). Since then, the relationship between protein phosphorylation and sleep regulation has been suggested by multiple genetic and biochemical findings—leading to the proposal of phosphorylation hypothesis of sleep (Ode

and Ueda, Front. Psychol. 2021). Phosphorylation/dephosphorylation-mediated protein regulation represents a promising target in sleep–wake regulation because it can occur on variable dynamics and time scale from minutes to hours (Sugai et al., Cell Rep. 2017; Yamaguchi et al., iScience 2021). Regarding CaMKII β , we found that CaMKII β promotes sleep by controlling sleep "induction" and "maintenance" according to its own phosphorylation states (Tone et al., PLOS Biol. 2022), and that CaMKII activity of PV-positive neurons, which constitute inhibitory neurons in the cortex, is important for the induction of rebound sleep after sleep deprivation (2024). Furthermore, we found that at excitatory postsynaptic sites, the protein phosphatase PKA promotes wakefulness and PP1 and calcineurin promote sleep, acting to competitively regulate sleep–wake cycles (Wang, Cao et al., Nature, 2024).

4) The development of “Human system biology” through the analysis of sleep–wake dynamics as a model platform

Do molecular mechanisms at the single amino acid residue level, such as specific protein phosphorylation, control the organism-level phenotype including human sleep–wake cycle? We will ask this question leveraging mouse genetics as a springboard to validate genotype–phenotype relationships.

We have elaborated our technology platforms for highly precise, large-scale, non-invasive measurements of sleep patterns, derived in mice, to humans. We developed a novel algorithm, ACCEL, which classifies sleep and wake with high sensitivity and specificity by using jerk of arm movement recorded by wristwatch-type accelerometers (Ode et al., iScience 2022). Using ACCEL, we estimated the sleep–wake dynamics from the arm acceleration data of 100,000 people registered in the UK biobank, and succeeded in classifying human sleep patterns into 16 types (Katori et al., PNAS 2022). Based on the ACCEL and sleep classification methods, we are working on social implementation of "sleep checkups" that will allow many people in our society to understand their own sleep status and trigger necessary changes in their own sleep behavior.

Humans provide a rich source of information on

the roles of genetic and environmental factors in sleep–wake control. We hope that our research results will contribute to the understanding of sleep disorders, circadian rhythm disorders, and associated psychiatric and neurodegenerative diseases, and to the search for therapeutic strategies.

References

1. Asai K, Kawahara S, Shirahata E, Iwasaki K, Nakai H, Kajiyama Y, Taniguchi S, Ge L, Kakuda K, Kimura Y, Miyahara T, Ueda HR, Ikenaka K, Mochizuki H. Evaluation of motor fluctuations in Parkinson's disease: electronic vs. conventional paper diaries. *Front. Neurol.* 15, 1476708 (2024)
2. Akiyama F, Matsumoto K, Yamashita K, Oishi A, Kitaoka T, Ueda HR. A multiwell plate approach to increase the sample throughput during tissue clearing. *Nat. Protoc.* advanced online publication
3. Wang Y, Cao S, Tone D, Fujishima H, Yamada RG, Ohno R, Shi S, Matsuzawa K, Yada S, Kaneko M, Sakamoto H, Onishi T, Ukai-Tadenuma M, Ukai H, Hanashima C, Hirose K, Kiyonari H, Sumiyama K, Ode KL, Ueda HR. Postsynaptic competition between calcineurin and PKA regulates mammalian sleep–wake cycles. *Nature* 636, 412–421 (2024)
4. Yanai R, Mitani TT, Susaki EA, Minamihisamatsu T, Shimojo M, Saito Y, Mizuma H, Nitta N, Kaneda D, Hashizume Y, Matsumoto G, Tanemura K, Zhang MR, Higuchi M, Ueda HR, Sahara N. A novel tauopathy model mimicking molecular and spatial aspects of human tau pathology. *Brain Commun.* 6, fcae326 (2024)
5. Chen YY, Evavold CL, Mann M, Davenport ER, McFall-Ngai M, Bienko M, Ueda HR, Tian L, Tjahjono N, Anikeeva P, Liu JG, Deans TL, Shen X. What tool or method do you wish existed? *Cell* 187, 4433–4438 (2024)
6. Yamada RG, Matsuzawa K, Ode KL, Ueda HR. An automated sleep staging tool based on simple statistical features of mice electroencephalography (EEG) and electromyography (EMG) data. *Eur. J. Neurosci.* 60, 5467–5486 (2024).
7. Kon K, Ode KL, Mano T, Fujishima H, Takahashi RR, Tone D, Shimizu C, Shiono S, Yada S, Matsuzawa K, Yoshida SY, Yoshida Garçon J, Kaneko M, Shinohara Y, Yamada RG, Shi S, Miyamichi K, Sumiyama K, Kiyonari H, Susaki EA, Ueda HR. Cortical parvalbumin neurons are responsible for homeostatic sleep rebound through CaMKII activation. *Nat. Commun.* 15, 6054 (2024)
8. Mitani TT, Susaki EA, Matsumoto K, Ueda HR. Realization of cellomics to dive into the whole-body or whole-organ cell cloud. *Nat. Methods* 21, 1138–1142 (2024)
9. Nonaka H, Sakamoto S, Shiraiwa K, Ishikawa M, Tamura T, Okuno K, Kondo T, Kiyonaka S, Susaki EA, Shimizu C, Ueda HR, Kakegawa W, Arai I, Yuzaki M, Hamachi I. Bioorthogonal chemical labeling of endogenous neurotransmitter receptors in living mouse brains. *Proc. Natl. Acad. Sci. U.S.A.* 121, e2313887121 (2024)
10. Millius A, Yamada RG, Fujishima H, Maeda K, Standley DM, Sumiyama K, Perrin D, Ueda HR. Circadian ribosome profiling reveals a role for the Period2 upstream open reading frame in sleep. *Proc. Natl. Acad. Sci. U.S.A.* 120, e2214636120 (2023)
11. Shintani-Domoto Y, Ode KL, Nomura S, Abe H, Ueda HR, Sakatani T, Ohashi R. Elucidation of the mechanism of amyloid A and transthyretin formation using mass spectrometry-based absolute quantification. *Virchows. Arch.* 120, e2214636120 (2023)

Pathology, Immunology and Microbiology

1. Pathology

Department of Pathology and Diagnostic Pathology

Professor

Tetsuo Ushiku, M.D., Ph.D.

Project Professor

Takeshi Sasaki, M.D., Ph.D. (Next-Generation Pathology Information Networking)

Associate Professor

Daizo Koinuma, M.D., Ph.D.

Aya Shinozaki-Ushiku, M.D., Ph.D. (Division of Integrative Genomics)

Lecturer

Masako Ikemura, M.D., Ph.D. (Office for “Promotion of CPC Education and General Integrative Medicine”)

Mariko Tanaka (Department of Pathology, Hospital)

Hiroyuki Abe, M.D., Ph.D.

Project Lecturer

Akiko Kunita, Ph.D. (Next-Generation Precision Medicine Development Laboratory)

Research Associate

Ryohei Kuroda, M.D., Ph.D., Masaki Suzuki, M.D., Ph.D., Munetoshi Hinata, M.D., Ph.D., Yoichi Yasunaga, M.D., Ph.D., Amane Yamamoto, M.D., Ph.D.

Akiko Takase, M.D., Ph.D., Mayu Hakozaiki, M.D., Ph.D., Atsushi Kondo, M.D., Ph.D.

Technical Support Specialist

Kei Sakuma, Kimiko Takeshita, M.T.

Homepage <http://pathol.umin.ac.jp/>

Introduction and Organization

Department of Pathology and Diagnostic Pathology is responsible for the practice of diagnostic pathology, education, and research in cooperation with Department of Pathology of the University Hospital. Our aim is to perform pathology as an important part of clinical medicine as well as to establish “next generation pathology” incorporating cutting-edge science and technology.

Dr. Rokutan resigned the position on March 31.

Dr Yamamoto joined as a research associate of the Department of Pathology of the hospital on Apr 1.

Three postgraduate students (Ideyama, Kishino and Asahina) finished the course and received Ph.D. In the new fiscal year, 2024, four new students will enter the postgraduate course, and there will be 12 postgraduates.

We are responsible for the pathology practice of the University of Tokyo Hospital and are carrying forward the morphology-based research targeting

human diseases. As for the education of the medical students, we take charge of the following courses: General Pathology Course for the 1st grade medical students in collaboration with Department of Molecular Pathology, Systemic Pathology for the 2nd grade, Elective Clinical Clerkship for the 4th grade, and Clinical Clerkship for the 3rd/4th grade students. Programs for postgraduates and junior residents are also included in our education activities.

"Tsunagu"- Fukushima-Kanto Pathology-Forensic Pathology Cooperation Program was planned in collaboration with Fukushima Medical University and Juntendo University, headed by Prof. Okabe, the former dean of Graduate School. The program has been adopted as one of Activation Program of Basic Researcher Training of the Ministry of Education, Culture, Sports, Science and Technology. During four years between FY2018 and FY2021, 13 postgraduate students were trained to be specialized in "death investigation, remote pathology diagnosis, and genomic medicine" with the training system oriented to region support by rotating among universities. We hope the students who joined this program will be future leaders in pathology and forensic medicine. We also hold an annual seminar to recruit high school students who aim to be pathologists and forensic scientists.

Teaching activities

We provide General Pathology Course for the 1st grade of undergraduate students, especially in morphology.

Each class of Systemic Pathology Course and exercises are held in parallel with that of Systemic Medicine Course. All the courses and exercises were conducted in person as those were before COVID-19, incorporating with the web system to access whole slide imaging. Students can look at pathology slides online, and this system works effectively in student education.

In Clinical Clerkship for all 3rd/4th grade medical students, following courses are included; autopsy pathologic practices with a case presentation by paired students, surgical pathologic practices using various tumor sections, and a tour of the pathology laboratory.

Both Clinical Clerkship course (4th grade) and

Free Quarter program (1st/2nd grade) accepted several students.

We also set up the lecture series of "Infection/Immunology/Cancer II" and "Tumor Pathology. We also provided an intensive exercise course, "Integration of Neuropathology/Radiology/Clinics".

Research activities

We explore the diagnosis and pathogenesis of disease, especially focusing on gastrointestinal oncogenesis. Ongoing project includes exploration of highly aggressive type of gastric cancer with fetal phenotype (e.g. AFP-producing gastric cancer) to clarify its pathogenesis, genomic abnormalities and to find therapeutic targets (Drs. Koinuma, Shinozaki-Ushiku, Kunita, Kuroda, Takase, Kondo and Yamamoto). We are also working on research projects of digestive system cancers, such as cancer immune microenvironment, Epstein-Barr virus-positive gastric cancer, hereditary gastric tumors, duodenal cancer (Dr. Shinozaki-Ushiku).

Our department has pathologists with different expertise, and they are engaged in specific research projects. The research covers brain tumors and neurodegenerative disease (Drs. Ikemura and Hakozaki), Epstein-Barr virus-associated neoplasms (Drs. Shinozaki-Ushiku, Abe and Hinata), liver and pancreatobiliary tumors (Drs. Tanaka and Yasunaga), and lung cancer (Dr. Suzuki). We also collaborate with other laboratories in and outside the University to develop new technologies such as AI, tissue clearing technique, and tissue processing robots in pathology practice (Drs. Abe and Hinata).

References

1. Abe H, Rokutan H, Totoki Y, Nakamura H, Shibata T, Ushiku T, Fukayama M. Lost expression of AT-rich interaction domain 1A in the gastric mucosa-A constituent of field cancerization in the stomach. *Pathol Int.* 2023; 73(6):234-245.
2. Arai J, Niikura R, Hayakawa Y, Hirata Y, Ushiku T, Fujishiro M. Autoimmune gastritis may be less susceptible to cancer development than *Helicobacter pylori*-related gastritis based

- on histological analysis. *Gut*. 2023;gutjnl-2023-330052.
3. Fukagawa A, Hama N, Totoki Y, Nakamura H, Arai Y, Saito-Adachi M, Maeshima A, Matsui Y, Yachida S, Ushiku T, Shibata T. Genomic and epigenomic integrative subtypes of renal cell carcinoma in a Japanese cohort. *Nat Commun*. 2023;14(1):8383.
 4. Hirata Y, Makino Y, Iida S, Katano H, Nagasawa S, Rokutan H, Hinata M, Iwasaki A, Yasunaga Y, Abe H, Ikemura M, Motomura A, Kira K, Kobayashi S, Tsuneya S, Torimitsu S, Yamamoto I, Nakagawa K, Hasegawa I, Akitomi S, Yajima D, Ushiku T, Saitoh H, Suzuki T, Iwase H. Analysis of COVID-19 in tissues acquired by minimally invasive autopsy in out-of-hospital deaths with postmortem degeneration. *Jpn J Infect Dis*. 2023;76(5):302-309.
 5. Kage H, Oda K, Muto M, Tsuchihara K, Okita N, Okuma Y, Kikuchi J, Shiota H, Hayashi H, Kokuryo T, Sakai D, Hirasawa A, Kubo M, Kenmotsu H, Akiyama N, Shinozaki-Ushiku A, Tanabe M, Ushiku T, Miyagawa K, Seto Y. Human resources for administrative work to carry out a comprehensive genomic profiling test in Japan. *Cancer Sci*. 2023;114(7):3041-3049.
 6. Kage H, Shinozaki-Ushiku A, Ishigaki K, Sato Y, Tanabe M, Tanaka S, Tanikawa M, Watanabe K, Kato S, Akagi K, Uchino K, Mitani K, Takahashi S, Miura Y, Ikeda S, Kojima Y, Watanabe K, Mochizuki H, Yamaguchi H, Kawazoe Y, Kashiwabara K, Kohsaka S, Tatsuno K, Ushiku T, Ohe K, Yatomi Y, Seto Y, Aburatani H, Mano H, Miyagawa K, Oda K. Clinical utility of Todai OncoPanel in the setting of approved comprehensive cancer genomic profiling tests in Japan. *Cancer Sci*. 2023;114(4):1710-1717.
 7. Kondo A, Shinozaki-Ushiku A (Co-first author), Rokutan H, Kunita A, Ikemura M, Yamashita H, Seto Y, Nagae G, Tatsuno K, Aburatani H, Koinuma D, Ushiku T. Loss of viral genome with altered immune microenvironment during tumour progression of Epstein-Barr virus-associated gastric carcinoma. *J Pathol*. 2023;260(2):124-136.
 8. Koyama H, Kurokawa R, Kato S, Ishida M, Kuroda R, Ushiku T, Kume H, Abe O. MR imaging features to predict the type of bone metastasis in prostate cancer. *Sci Rep*. 2023; 13(1):11580.
 9. Kusakabe M, Taguchi A, Tanikawa M, Hoshi D, Tsuchimochi S, Qian X, Toyohara Y, Kawata A, Wagatsuma R, Yamaguchi K, Yamamoto Y, Ikemura M, Sone K, Mori-Uchino M, Matsunaga H, Tsuruga T, Nagamatsu T, Kukimoto I, Wada-Hiraike O, Kawazu M, Ushiku T, Takeyama H, Oda K, Kawana K, Hippo Y, Osuga Y. Application of organoid culture from HPV18-positive small cell carcinoma of the uterine cervix for precision medicine. *Cancer Med*. 2023; 12(7):8376-8489.
 10. Masugi Y, Takamatsu M, Tanaka M (Co-first author), Hara K, Inoue Y, Hamada T, Suzuki T, Arita J, Hirose Y, Kawaguchi Y, Nakai Y, Oba A, Sasahira N, Shimane G, Takeda T, Tateishi K, Uemura S, Fujishiro M, Hasegawa K, Kitago M, Takahashi Y, Ushiku T, Takeuchi K, Sakamoto M; GTK Pancreatic Cancer Study Group in Japan. Post-operative mortality and recurrence patterns in pancreatic cancer according to KRAS mutation and CDKN2A, p53, and SMAD4 expression. *J Pathol Clin Res*. 2023;9(5):339-353.
 11. Matsubara D, Yoshimoto T, Akolekar N, Totsuka T, Amano Y, Kihara A, Miura T, Isagawa Y, Sakuma Y, Ishikawa S, Ushiku T, Fukayama M, Niki T. Genetic and phenotypic determinants of morphologies in 3D cultures and xenografts of lung tumor cell lines. *Cancer Sci*. 2023;114(4): 1757-1770.
 12. Nakatsuka T, Nakagawa H, Uchino K, Rokutan H, Tanaka M, Moriyama M, Fukumoto T, Yamada T, Wake T, Nakagomi R, Sato M, Minami T, Kudo Y, Ushiku T, Fujishiro M, Tateishi R. Clinical utility of postablation liver tumor biopsy and possibility of gene mutation analysis. *Hepatol Res*. 2023;53(11):1117-1125.
 13. Nakai K, Lin H, Yamano S, Tanaka S, Kitamoto S, Saitoh H, Sakuma K, Kurauchi J, Akter E, Konno M, Ishibashi K, Kamata R, Ohashi A, Koseki J, Takahashi H, Yokoyama H, Shiraki Y, Enomoto A, Abe S, Hayakawa Y, Ushiku T, Mutoh M, Fujita Y, Kon S. Wnt activation disturbs cell competition and causes diffuse invasion of transformed cells through NF- κ B-

- MMP21 pathway. *Nat Commun.* 2023;14(1):7048.
14. Nakaya M, Nakai Y, Takahashi M, Fukukura Y, Sato K, Kameda A, Tashiro Y, Kageyama S, Sofue K, Nakano T, Yoshimitsu K, Marugami N, Takeyama N, Tanaka M, Hasegawa K, Watadani T. Intraductal oncocytic papillary neoplasm of the pancreas: clinical and radiological features compared to those of intraductal papillary mucinous neoplasm. *Abdom Radiol (NY)*. 2023; 48(8):2483-2493.
 15. Okuno K, Torimoto K, Kuroda R(Co-first author), Cicalese SM, Okuno Y, Kono R, Marumoto S, Utsunomiya H, Eguchi S. Infused juice concentrate of Japanese plum *Prunus mume* attenuates inflammatory vascular remodeling in a mouse model of hypertension induced by angiotensin II. *Hypertension research*. 2023; 46(8):1923-1933.
 16. Oyama H, Hamada T, Nakai Y, Tanaka M, Endo G, Hakuta R, Ishida K, Ishigaki K, Kanai S, Kurihara K, Saito T, Sato T, Suzuki T, Suzuki Y, Takaoka S, Tange S, Tokito Y, Takahara N, Ushiku T, Fujishiro M. Clinical trajectory of intraductal papillary mucinous neoplasms progressing to pancreatic carcinomas during long-term surveillance: a prospective series of 100 carcinoma cases. *J Gastroenterol*. 2023; 58(10):1068-1080.
 17. Saitoh H, Sakai-Tagawa Y, Nagasawa S, Torimitsu S, Kubota K, Hirata Y, Iwatsuki-Horimoto K, Motomura A, Ishii N, Okaba K, Horioka K, Abe H, Ikemura M, Rokutan H, Hinata M, Iwasaki A, Yasunaga Y, Nakajima M, Yamaguchi R, Tsuneya S, Kira K, Kobayashi S, Inokuchi G, Chiba F, Hoshioka Y, Mori A, Yamamoto I, Nakagawa K, Katano H, Iida S, Suzuki T, Akitomi S, Hasegawa I, Ushiku T, Yajima D, Iwase H, Makino Y, Kawaoka Y. High titers of infectious SARS-CoV-2 in corpses of patients with COVID-19. *Int J Infect Dis*. 2023;129:103-109.
 18. Suzuki M, Kasajima R, Yokose T, Shimizu E, Hatakeyama S, Yamaguchi K, Yokoyama K, Katayama K, Yamaguchi R, Furukawa Y, Miyano S, Imoto S, Shinozaki-Ushiku A, Ushiku T, Miyagi Y. KMT2C expression and DNA homologous recombination repair factors in lung cancers with a high-grade fetal adenocarcinoma component. *Trans Lung Cancer Res*. 2023;12(8):1738-1751.
 19. Totoki Y, Saito-Adachi M, Shiraishi Y, Komura D, Nakamura H, Suzuki A, Tatsuno K, Rokutan H, Hama N, Yamamoto S, Ono H, Arai Y, Hosoda F, Katoh H, Chiba K, Iida N, Nagae G, Ueda H, Shihang C, Sekine S, Abe H, Nomura S, Matsuura T, Sakai E, Ohshima T, Rino Y, Yeoh KG, So J, Sanghvi K, Soong R, Fukagawa A, Yachida S, Kato M, Seto Y, Ushiku T, Nakajima A, Katai H, Tan P, Ishikawa S, Aburatani H, Shibata T. Multiancestry genomic and transcriptomic analysis of gastric cancer. *Nat Genet*. 2023;55(4):581-594.
 20. Tsubosaka A, Komura D, Kakiuchi M, Katoh H, Onoyama T, Yamamoto A, Abe H, Seto Y, Ushiku T, Ishikawa S. Stomach encyclopedia: Combined single-cell and spatial transcriptomics reveal cell diversity and homeostatic regulation of human stomach. *Cell Rep*. 2023;42(10):113236.
 21. Yamaguchi K, Horie C, Takane K, Ikenoue T, Nakagawa S, Isobe Y, Ota Y, Ushiku T, Tanaka M, Fujishiro J, Hoshino N, Arisue A, Nishizuka S, Aikou S, Shida D, Furukawa Y. Identification of odontogenic ameloblast associated as a novel target gene of the Wnt/ β -catenin signaling pathway. *Cancer Sci*. 2023;114(3):948-960.
 22. Yamashita S, Abe H, Yamashita H, Yagi K, Seto Y, Ushiku T. PD-L1 and HLA-class I expression status and their therapeutic implication in oesophageal small-cell carcinoma. *Histopathology*. 2023; 83(2):264-275.

Department of Molecular Pathology

Professor

Yasuhiro Yamada, M.D., Ph.D.

Associate professor

Yosuke Yamada, M.D., Ph.D.

Assistant professors

Sho Ohta, Ph.D., Nao Sankoda, M.D., Ph.D.

Homepage http://molpathology2.m.u-tokyo.ac.jp/home_E/index.html

Introduction and Organization

The Department of Molecular Pathology has a history of more than 120 years, originating from the Second Department of Pathology, of which the first professor was Dr Katsusaburo Yamagiwa, who succeeded in inducing artificial cancer by applying coal tar to rabbit ears. In November 2022, Yasuhiro Yamada was transferred from the Institute of Medical Science, University of Tokyo, to succeed Professor Kohei Miyazono, who retired in March 2022. The department has been conducting basic research on cancer at the organismal level as well as research on tissue regeneration and aging. As of the end of March 2024, the department comprised one professor, one associate professor, and two assistant professors, in addition to four researchers, seven postgraduate students, and two technical experts.

Teaching activities

Our department takes responsibility for lectures on “General Pathology” for undergraduate students of the Faculty of Medicine in collaboration with the Department of Human Pathology. Since we believe it is very important for medical students to study basic oncology, we teach basic tumor biology in our lectures on General Pathology. Given that the function of oncogenes and cancer-suppressor genes, the mechanism of viral

carcinogenesis, cancer epidemiology, cancer genetics, the mechanism of cancer invasion and metastasis as well as cancer epigenetics are important issues in cancer biology, we give intensive lectures on these topics. Practical training included experiments on immunostaining of tumor tissue. During systematic lectures on oncology, we hope that undergraduate students will get an overview of cancer biology. We also supervise the research activities of the graduate students of the department.

Our laboratory is located on the 11th floor of the Research Building of the Graduate School of Medicine. The Department of Molecular Pathology holds weekly progress meetings in the department and a weekly journal club to provide research guidance to students.

Research activities

Epigenetic regulation plays a critical role in cell fate specification during normal development and stable maintenance of somatic cell fate. Impairment in epigenetic regulation is often associated with various diseases such as cancer. Recent studies also imply that altered epigenetic regulation is involved in cells of aged organisms. Together, maintaining proper epigenetic regulation is crucial for the healthy life of organisms.

The development of reprogramming technologies, as

represented by iPS cell derivation, has enabled to control of somatic cell fate. The reprogramming process involves dynamic changes in epigenetic modifications. Taking advantage of reprogramming technology, we have devised reprogrammable mouse models in which epigenetic regulation and eventually cell fate can be altered in vivo. By inducing perturbation of epigenetic regulation and a cellular identity at the organismal level, we aim to elucidate the impact of epigenetic regulation on pathogenesis and aging. Finally, we aim to develop a means for disease treatment, tissue regeneration, and rejuvenation through epigenetic regulation with reprogramming technologies.

Our effort should promote interdisciplinary research that connects a wide range of research fields, which eventually contributes to the development of novel strategies to control the detrimental effects of diseases and aging in humans.

From 2017, our research has been supported by a CREST program “Clarification of the Mechanism of Individual’s Functional Impairment over the Entire Life Course” from Japan Agency for Medical Research and Development (AMED) (22gm1110004h9906). From 2022, our research is also supported by a Project for Promotion of Cancer Research and Therapeutic Evolution (P-PROMOTE) (22ama221201h0001) and by a Research Center Network for Realization of Regenerative Medicine (22bm1223002h0001), both from AMED.

Followings are research projects conducted at our laboratory in 2022.

1) Dissecting cancer biology with reprogramming technology

Epigenetic regulation plays a critical role in the cellular differentiation, the stable maintenance of cellular identity, and the reprogramming process. Accumulating evidence suggests that epigenetic abnormalities represented by abnormal DNA methylation have been involved in various diseases. We are interested in unveiling epigenetic regulation in cellular differentiation, the maintenance of cellular identity, and the pathogenesis including cancer. Taking

advantage of reprogramming technology, we have devised reprogrammable mouse models in which epigenetic regulation and eventually cell fate can be altered in vivo. By analyzing in vivo reprogramming process, we aim to uncover the epigenetic regulation in cancer development, cancer cell maintenance, and progression. Finally, we will try to develop a novel approach targeting epigenetic regulation to treat cancer patients.

2) In vivo reprogramming for tissue regeneration and rejuvenation

We have devised in vivo reprogramming systems (Reprogrammable Mouse) in which iPS cells can be induced in living mice. Recent analyses of Reprogrammable Mice have revealed unappreciated mechanisms regarding senescence, tissue regeneration, and rejuvenation. By analyzing the response to cell fate perturbations at the organismal level, we aim to clarify the molecular basis of aging and tissue regeneration. Furthermore, we apply these reprogramming systems to develop innovative strategies for tissue regeneration and rejuvenation.

3) Expansion of mature islet cells as a regenerative strategy targeting diabetes

We showed that a MYCL-mediated reprogramming expands functional islet cells. We aim to apply these methods to islet transplantation therapy through amplification of cadaveric islet cells in vitro. We also try to induce the proliferation of mature islet cells in vivo by gene therapy. The goal of our study is to develop regenerative medicine and restore the function of aging pancreatic islets using reprogramming technology.

References

- 1 Hirano M, Yamada Y. Reprogramming of pancreatic islet cells for regeneration and rejuvenation. *Curr. Opin. Genet. Dev.* 2023 doi:10.1016/j.gde.2023.102099
- 2 Ohta S, Yamada Y. Exploring the potential of in vivo reprogramming for studying embryonic development, tissue regeneration, and organismal aging. *Curr. Opin. Genet. Dev.* 2023 doi: 10.1016/j.gde.2023.102067

Pathology, Immunology and Microbiology

2. Microbiology

Department of Microbiology

Professor

Makoto Takeda, M.D., Ph.D.

Associate Professor

Hiroshi Katoh, Ph.D.

Associate

Yukiko Akahori, Ph.D., Yuki Kitai, , Ph.D.,

Homepage <https://microbiology.labby.jp>

Introduction and Organization

As of April 2023, Assistant Professor Yuki Kitai has newly joined our laboratory. With this addition, our team now consists of four members: one Professor (Takeda), one Associate Professor (Katoh), and two Assistant Professors (Akahori and Kitai). Together, we are dedicated to our daily research and educational activities.

Teaching activities

In a series of lectures (totaling 64 hours) and laboratory courses (36 hours), the following topics are covered:

1. Molecular biology of bacteria, phages, and animal viruses
2. Mechanisms of microbial diseases
3. Laboratory diagnosis of pathogenic microbes
4. Infection control and biosafety
5. Applications of microbial organisms in biotechnology
6. Socioeconomic impact of microbial diseases

Research activities

Our laboratory focuses primarily on paramyxoviruses and other respiratory viruses such as coronaviruses and influenza viruses. We aim to contribute to society by deepening the understanding of the molecular mechanisms underlying viral diseases. Additionally, we strive to advance modern medicine by developing innovative technologies related to recombinant viruses.

In our research on the replication and pathogenic mechanisms of paramyxoviruses, we investigate host factors essential for the intracellular replication of viruses such as measles and mumps viruses. By elucidating the interactions between these host factors and viral components, we seek to uncover how these viruses cause disease.

In the study of activation mechanisms of respiratory viruses by host proteases, we have demonstrated that the membrane fusion proteins of various respiratory viruses, including the novel coronavirus SARS-CoV-2, are activated by TMPRSS2, a protease found in host cells.

Furthermore, leveraging the genetic manipulation techniques for paramyxoviruses that we have refined over many years, we are advancing applied research, including developing viral vectors and vaccines.

The role of host protease TMPRSS2 in SARS-CoV-2 infection

In cultured cells, SARS-CoV-2 can infect cells through multiple pathways utilizing different host proteases. Our research, which includes studies using TMPRSS2 knockout mice, has demonstrated that the infection pathway utilizing furin and TMPRSS2 (the early entry pathway) is particularly critical for SARS-CoV-2 infection. However, recent studies have reported that this early entry pathway is not as essential for the infection of Omicron variants, which have become predominant in recent outbreaks. Instead, these

variants primarily use the late entry pathway involving cathepsins within endosomes.

Our findings also confirm that Omicron variants predominantly rely on the late entry pathway for infection. Nevertheless, we discovered that through successive mutations, Omicron variants have gradually regained the ability to utilize TMPRSS2.

Furthermore, respiratory organoid analyses revealed that SARS-CoV-2 infection does not rely solely on TMPRSS2. The endocytic pathway mediated by cathepsins also plays a significant role, highlighting the complexity and adaptability of the virus's infection mechanisms.

Structural and molecular properties of mumps virus inclusion bodies

Viral RNA synthesis of mumps virus (MuV) occurs in a cytoplasmic membrane-less organelle called the inclusion body (IB). The MuV IBs had characteristics of liquid organelles: they are spherical, they fuse to form larger structures and their liquid phase is confirmed by FRAP experiments. Further detailed observation of the internal structure using super-resolution microscopy revealed that IBs are web-like structures formed by viral nucleocapsid protein and phosphoprotein (P protein) and that viral polymerase co-localizes with viral RNAs within the IBs. Next, we searched for host RNAs recruited to the MuV IB by spatial transcriptome analysis and found that RNAs containing guanine quadruplex motif sequences (G4-RNA) accumulate in the IB. *In vitro* LLPS assays revealed that G4-RNA interacts with the P protein and promotes molecular condensation inside the droplet formed by the P protein.

Involvement of host protease TMPRSS2 in RS virus Infection

RS virus causes respiratory tract infections, especially in children. Activation of membrane fusion proteins by host proteases is required for the virus to acquire infectivity. Until now, it has been assumed that the host protease furin is important for activating the RS virus membrane fusion protein (F protein). However, recent studies have suggested the involvement of other proteases as well. Therefore, we focused on TMPRSS2, a host protease highly expressed in respiratory tissues that contributes to the activation of other respiratory

viruses, and analyzed its involvement in RS virus infection.

In cells stably expressing TMPRSS2, RS virus replication and syncytia formation by cell fusion, characteristic of RS virus-infected cells, were enhanced. Detailed analysis indicated that the involvement of TMPRSS2 was negative for the activation of F proteins biosynthesized in infected cells, suggesting that TMPRSS2 may activate F proteins at the stage of virus entry. In addition, RS virus-infected cells showed enhanced cell fusion ability to TMPRSS2-expressing cells. These results indicate that TMPRSS2 may contribute to RS virus infection of respiratory tissues.

References

1. Bae C, Katoh H, Wakata A, Sakata M, Kato F, Takeda M. Demonstration of bacterium-free very rapid reverse genetics system using mumps virus. *Microbiol Immunol* 67:44-47, 2023.
2. Miyano S, Vynnycky E, Pattamavone C, Ichimura Y, Mori Y, Nouanthong P, Phounphenghack K, Tengbriacheu C, Khamphaphongphane B, Franzel L, Yang TU, Raaijmakers H, Komada K, Ota T, Funato M, Takeda M, Hachiya M: Comparison of population-based measles-rubella immunoglobulin G antibody prevalence between 2014 and 2019 in Lao People's Democratic Republic: Impacts of the national immunization program. *Int J Infect Dis* 129:70-77, 2023.
3. Okura T, Tahara M, Otsuki N, Sato M, Takeuchi K, Takeda M: Generation of a photocontrollable recombinant bovine parainfluenza virus type 3. *Microbiol Immunol* 67:204-209, 2023.
4. Ono T, Hashimoto K, Kume Y, Chishiki M, Okabe H, Sato M, Norito S, Aso J, Sada M, Mochizuki I, Mashiyama F, Ishibashi N, Suzuki S, Sakuma H, Suwa R, Kawase M, Takeda M, Shirato K, Kimura H, Hosoya M: Molecular Diversity of Human Respiratory Syncytial Virus before and during the COVID-19 Pandemic in Two Neighboring Japanese Cities. *Microbiol Spectr* 11:e0260622, 2023.
5. Someya K, Okemoto-Nakamura Y, Kurata T, Kanbayashi D, Saito N, Itamochi M, Otsuki N, Hanada K, Takeda M. Establishment of measles virus receptor-expressing Vero cells lacking functional poliovirus receptors. *Microbiol Immunol*.

67:166-170, 2023.

6. Takahashi T, Akagawa M, Kimura R, Sada M, Shirai T, Okayama K, Hayashi Y, Kondo M, Takeda M, Ryo A, Kimura H: Molecular evolutionary analyses of the fusion protein gene in human respirovirus 1. *Virus Res* 333:199142, 2023.
7. Takashita E, Fujisaki S, Morita H, Nagata S, Miura H, Nagashima M, Watanabe S, Takeda M, Kawaoka Y, Hasegawa H: Assessment of the frequency of SARS-CoV-2 Omicron variant escape from RNA-dependent RNA polymerase inhibitors and 3C-like protease inhibitors. *Antiviral Res* 216:105671, 2023.

Department of Infection Control and Prevention

Professor

Takeya Tsutsumi, M.D., Ph.D.

Lecturer

Nobuhiko Satoh, M.D., Ph.D.

Project Lecturer

Kazuya Okushin, M.D., Ph.D.

Research Associate

Mayo Tsuboi, M.D., Ph.D.

Daisuke Ohki, M.D., Ph.D.

Ryu Yoneda, M.D., Ph.D.

Homepage <http://square.umin.ac.jp/ut-ict/>

Introduction and Organization

The Department of Infection Control and Prevention started at first as the Division of Hospital Infection Control Services on January 23, 1991. This division developed into the Division of Infection Control and Prevention on September 1, 1993 and the present department on June 4, 1994. Currently, our faculty consists of one professor, one lecturer, five research associates, 12 laboratory technicians, and two office assistants. For isolation and identification of microorganisms from clinical specimens, we amalgamated the microbiology unit from the Department of Clinical Laboratory in 2001.

Clinical activities

Our daily activities are as follows:

- 1) Surveillance and control of hospital-acquired infection, such as infection or colonization of methicillin-resistant *Staphylococcus aureus* and other drug-resistant microbes.
- 2) Investigation of trends in weekly bases and monthly reports to all departments; Screening of

colonization; monitoring of appropriate use of antibiotics.

- 3) Microbiological investigation of wards and environment.
- 4) Detection, investigation, intervention and control of the hospital infection outbreak.
- 5) Offering of information and advice on HIV-infected patients' management.
- 6) Direct inquiries and advises on management of patients with various infections through ward rounds every week.

Education

We have been charged for education of undergraduate students on the course of medicine (lectures and practical exercises on the infection control for the 4th grade students). These lectures and exercises contain subjects not only on the hospital infection but also on clinical microbiology. We are also engaged in the education of graduate students as well as hospital staff.

For postgraduate education, we have been committed

to the guidance for new postgraduates and residents on the hospital and occupational infection control. We have been also offering our information and technique on occasions of request.

Research activities

We have been mainly studying on following subjects: Several studies are now going with the members of department of pharmacy and of surgery.

- 1) Development of preemptive strategies for the control of healthcare-associated infection
- 2) Development of new methods in infection control and treatment of viral hepatitis
- 3) Mechanisms and molecular epidemiology of multi-drug resistant microorganisms
- 4) Clinical characteristics and molecular epidemiology of hypervirulent *Klebsiella pneumoniae* infection
- 5) Prevention and therapy for COVID-19
- 6) Epidemiology of *Clostridioides difficile* infection
- 7) Molecular epidemiological analysis of MRSA
- 8) Prevention of endoscope-related infection
- 9) Usefulness of environmental monitoring

Publications

1. Ikeda M, Kobayashi T, Okugawa S, Fujimoto F, Okada Y, Tatsuno K, Higurashi Y, Tsutsumi T, Moriya K. Comparison of phylogenetic and virulence factors between *Escherichia coli* isolated from biliary tract infections and uropathogenic *Escherichia coli*. *Heliyon*. 2023; 9(11):e21748.
2. Ikeuchi K, Saito M, Adachi E, Koga M, Okushin K, Tsutsumi T, Yotsuyanagi H. Injection drug use and sexually transmitted infections among men who have sex with men: A retrospective cohort study at an HIV/AIDS referral hospital in Tokyo, 2013-2022. *Epidemiol Infect*. 2023;151:e195.
3. Uraki R, Ito M, Kiso M, Yamayoshi S, Iwatsuki-Horimoto K, Sakai-Tagawa Y, Imai M, Koga M, Yamamoto S, Adachi E, Saito M, Tsutsumi T, Otani A, Fukushi S, Watanabe S, Suzuki T, Kikuchi T, Yotsuyanagi H, Maeda K, Kawaoka Y. Antiviral efficacy against and replicative fitness of an XBB.1.9.1 clinical isolate. *iScience*. 2023;26(11):108147.
4. Kawase K, Okamoto K, Harada S, Nomura Y, Shimada S, Komae H, Kuroda R, Ideyama M, Soma K, Mizoguchi M, Higurashi Y, Ukai K, Adachi-Katayama M, Miwa T, Wakimoto Y, Oyabu T, Jubishi D, Hashimoto H, Okugawa S, Ono M, Doi K, Ushiku T, Tsutsumi T. A case of hypervirulent K1-ST23 *Klebsiella pneumoniae* endocarditis and papillary muscle rupture secondary to multiple site abscesses. *J Infect Chemother*. 2024;30(2):154-8.
5. Kado A, Tsutsumi T, Yotsuyanagi H, Ikeuchi K, Okushin K, Moriya K, Koike K, Fujishiro M. Noninvasive approach to indicate risk factors of nonalcoholic steatohepatitis overlapping autoimmune hepatitis based on peripheral lymphocyte pattern. *J Gastroenterol*. 2023; 58(12):1237-51.
6. Adachi E, Saito M, Kikuchi T, Ikeuchi K, Koga M, Tsutsumi T, Yotsuyanagi H. Incidence of sexually transmitted hepatitis C virus infection among men who have sex with men in Japan from 2009 to 2023. *J Med Virol*. 2023;95(8): e29039.
7. Okushin K, Kurano M; UTH-UDCA Study Group; Yatomi Y, Moriya K, Fujishiro M, Tsutsumi T. Ursodeoxycholic acid for coronavirus disease 2019 prevention. *J Intern Med*. 2024;295(1):106-9.
8. Yamamoto S, Yamayoshi S, Ito M, Sakai-Tagawa Y, Nakachi I, Baba R, Kamimoto S, Ogura T, Hagiwara S, Kato H, Nakajima H, Uwamino Y, Yagi K, Sugaya N, Nagai H, Saito M, Adachi E, Koga M, Tsutsumi T, Duong C, Okuda M, Murakami J, Furusawa Y, Ujie M, Iwatsuki-Horimoto K, Yotsuyanagi H, Kawaoka Y. Differences among epitopes recognized by neutralizing antibodies induced by SARS-CoV-2 infection or COVID-19 vaccination. *iScience*. 2023;26(7):107208.
9. Ishizaka A, Koga M, Mizutani T, Uraki R, Yamayoshi S, Iwatsuki-Horimoto K, Yamamoto S, Imai M, Tsutsumi T, Suzuki Y, Kawaoka Y, Yotsuyanagi H. Research article antibody induction and immune response in nasal cavity by third dose of SARS-CoV-2 mRNA vaccination. *Virol J*. 2023;20(1):146.

10. Okugawa S, Ikeda M, Kashiwabara K, Moritoyo T, Kohsaka T, Shimizu T, Hagiya H, Hasegawa K, Otsuka F, Miwa A, Kisimoto N, Mizoguchi A, Imamura A, Ikeuchi K, Tsutsumi T, Jubishi D, Hashimoto H, Okamoto K, Harada S, Inoue JI, Seto Y, Moriya K. Antiviral effect and safety of nafamostat mesilate in patients with mild early-onset COVID-19: An exploratory multicentre randomized controlled clinical trial. *Int J Antimicrob Agents*. 2023;62(3):106922.
11. Okushin K, Yamana H, Tateishi R, Sato M, Tsutsumi T, Matsui H, Fushimi K, Yasunaga H, Koike K, Fujishiro M. Treatment and outcome of hepatorenal syndrome in Japan: a retrospective cohort study using a national inpatient database. *BMC Gastroenterol*. 2023;23(1):218.
12. Uraki R, Ito M, Kiso M, Yamayoshi S, Iwatsuki-Horimoto K, Sakai-Tagawa Y, Imai M, Koga M, Yamamoto S, Adachi E, Saito M, Tsutsumi T, Otani A, Kashima Y, Kikuchi T, Theiler J, Yotsuyanagi H, Suzuki Y, Korber B, Kawaoka Y. Efficacy of antivirals and mRNA vaccination against an XBF clinical isolate. *Lancet Reg Health West Pac*. 2023;34:100777.
13. Ikeuchi K, Tsutsumi T, Ishizaka A, Mizutani T, Sedohara A, Koga M, Tamaoki S, Yotsuyanagi H. Modulation of duodenal and jejunal microbiota by rifaximin in mice with CCl₄-induced liver fibrosis. *Gut Pathog*. 2023;15(1):14.
14. Yamaguchi R, Yamamoto T, Okamoto K, Harada S, Echizenya M, Tsutsumi T, Takada T. Teicoplanin and vancomycin as treatment for glycopeptide-susceptible *Enterococcus faecium* bacteraemia: a propensity score-adjusted non-inferior comparative study. *J Antimicrob Chemother*. 2023;78(5):1231-40.
15. Bramer LM, Hontz RD, Einfeld AJ, Sims AC, Kim YM, Stratton KG, Nicora CD, Gritsenko MA, Schepmoes AA, Akasaka O, Koga M, Tsutsumi T, Nakamura M, Nakachi I, Baba R, Tateno H, Suzuki S, Nakajima H, Kato H, Ishida K, Ishii M, Uwamino Y, Mitamura K, Paurus VL, Nakayasu ES, Attah IK, Letizia AG, Waters KM, Metz TO, Corson K, Kawaoka Y, Gerbasi VR, Yotsuyanagi H, Iwatsuki-Horimoto K. Multi-omics of NET formation and correlations with CNDP1, PSPB, and L-cystine levels in severe and mild COVID-19 infections. *Heliyon*. 2023;9(3):e13795.
16. Uraki R, Ito M, Kiso M, Yamayoshi S, Iwatsuki-Horimoto K, Sakai-Tagawa Y, Furusawa Y, Imai M, Koga M, Yamamoto S, Adachi E, Saito M, Tsutsumi T, Otani A, Kashima Y, Kikuchi T, Yotsuyanagi H, Suzuki Y, Kawaoka Y. Efficacy of antivirals and bivalent mRNA vaccines against SARS-CoV-2 isolate CH.1.1. *Lancet Infect Dis*. 2023;23(5):525-6.
17. Kado A, Inoue Y, Moriya K, Tsutsumi T, Ikeuchi K, Okushin K, Yotsuyanagi H, Koike K, Fujishiro M. Triglyceride level and soft drink consumption predict nonalcoholic fatty liver disease in nonobese male adolescents. *Hepatol Res*. 2023;53(6):497-510.
18. Uraki R, Ito M, Kiso M, Yamayoshi S, Iwatsuki-Horimoto K, Furusawa Y, Sakai-Tagawa Y, Imai M, Koga M, Yamamoto S, Adachi E, Saito M, Tsutsumi T, Otani A, Kikuchi T, Yotsuyanagi H, Halfmann PJ, Pekosz A, Kawaoka Y. Antiviral and bivalent vaccine efficacy against an omicron XBB.1.5 isolate. *Lancet Infect Dis*. 2023;23(4):402-3.
19. Tanaka T, Koga M, Tsutsumi T, Hosaka T, Yotsuyanagi H. Some people living with HIV might need to pay attention to their mental health during the COVID-19 two years pandemic in Tokyo until the Omicron variant occur. *PCN Rep*. 2023;2(1):e73.
20. Ikeda M, Okugawa S, Kashiwabara K, Moritoyo T, Kanno Y, Jubishi D, Hashimoto H, Okamoto K, Tsushima K, Uchida Y, Mitsumura T, Igari H, Tsutsumi T, Araoka H, Yatera K, Yamamoto Y, Nakamura Y, Otani A, Yamashita M, Wakimoto Y, Shinohara T, Adachi-Katayama M, Oyabu T, Kanematsu A, Harada S, Takeshita Y, Nakano Y, Miyazaki Y, Sakao S, Saito M, Ogura S, Yamasaki K, Kawasuji H, Hataji O, Inoue JI, Seto Y, Moriya K. Multicenter, single-blind, randomized controlled study of the efficacy and safety of favipiravir and nafamostat mesilate in patients with COVID-19 pneumonia. *Int J Infect Dis*. 2023;128:355-63.
21. Uraki R, Ito M, Furusawa Y, Yamayoshi S, Iwatsuki-Horimoto K, Adachi E, Saito M, Koga M, Tsutsumi T, Yamamoto S, Otani A, Kiso M,

- Sakai-Tagawa Y, Ueki H, Yotsuyanagi H, Imai M, Kawaoka Y. Humoral immune evasion of the omicron subvariants BQ.1.1 and XBB. *Lancet Infect Dis.* 2023;23(1):30-2.
22. Aoki T, Yamada A, Oka S, Tsuboi M, Kurokawa K, Togo D, Tanino F, Teshima H, Saito H, Suzuki R, Arai J, Abe S, Kondo R, Yamashita A, Tsuboi A, Nakada A, Niikura R, Tsuji Y, Hayakawa Y, Matsuda T, Nakahori M, Tanaka S, Kato Y, Tada T, Fujishiro M. Comparison of clinical utility of deep learning-based systems for small-bowel capsule endoscopy reading. *J Gastroenterol Hepatol.* 2024;39(1):157-64.
 23. Niikura R, Hayakawa Y, Nagata N, Miyoshi-Akiyama T, Miyabayashi K, Tsuboi M, Suzuki N, Hata M, Arai J, Kurokawa K, Abe S, Uekura C, Miyoshi K, Ihara S, Hirata Y, Yamada A, Fujiwara H, Ushiku T, Woods SL, Worthley DL, Hatakeyama M, Han YW, Wang TC, Kawai T, Fujishiro M. Non-*Helicobacter pylori* Gastric Microbiome Modulates Prooncogenic Responses and Is Associated With Gastric Cancer Risk. *Gastro Hep Adv.* 2023;2(5):684-700.
 24. Kawamura T, Sekiguchi M, Takamaru H, Mizuguchi Y, Horiguchi G, Toyozumi H, Kato M, Kobayashi K, Sada M, Oda Y, Yokoyama A, Utsumi T, Tsuji Y, Ohki D, Takeuchi Y, Shichijo S, Ikematsu H, Matsuda K, Teramukai S, Kobayashi N, Matsuda T, Saito Y, Tanaka K. Endoscopist-related factors affecting adenoma detection during colonoscopy: Data from the J-SCOUT study. *Dig Endosc.* 2024;36(1):51-8.
 25. Nagao S, Takahashi Y, Denda T, Tanaka Y, Miura Y, Mizutani H, Ohki D, Sakaguchi Y, Yakabi S, Tsuji Y, Niimi K, Kakushima N, Yamamichi N, Ota Y, Koike K, Fujishiro M. Reduced DEFA5 Expression and STAT3 Activation Underlie the Submucosal Invasion of Early Gastric Cancers. *Digestion.* 2023;104(6):480-93.
 26. Sakaguchi Y, Tsuji Y, Sato J, Kubota D, Obata M, Cho R, Nagao S, Miura Y, Ohki D, Mizutani H, Yakabi S, Kakushima N, Niimi K, Fujishiro M. Repeated steroid injection and polyglycolic acid shielding for prevention of refractory esophageal stricture. *Surg Endosc.* 2023;37(8):6267-77.
 27. Mizutani S, Takahashi Y, Shimamoto T, Nakagawa H, Hisada H, Oshio K, Kubota D, Mizutani H, Ohki D, Sakaguchi Y, Yakabi S, Niimi K, Kakushima N, Tsuji Y, Wada R, Yamamichi N, Fujishiro M. Performing the ABC Method Twice for Gastric Cancer Risk Stratification: A Retrospective Study Based on Data from a Large- Scale Screening Facility. *Diagnostics (Basel).* 2023;13(7):1284.
 28. Sakaguchi Y, Saito Y, Ando M, Yoshida M, Fukuoka O, Kobayashi K, Kubota D, Ohki D, Mizutani H, Niimi K, Tsuji Y, Fujishiro M, Yamasoba T. Risk factors for incomplete resection with pharyngeal endoscopic sub-mucosal dissection and long- term prognosis after resection. *Surg Endosc.* 2023;37(5):3593-601.
 29. Kawamura T, Sekiguchi M, Takamaru H, Mizuguchi Y, Horiguchi G, Kato M, Kobayashi K, Sada M, Oda Y, Yokoyama A, Utsumi T, Tsuji Y, Ohki D, Takeuchi Y, Shichijo S, Ikematsu H, Matsuda K, Teramukai S, Kobayashi N, Matsuda T, Saito Y, Tanaka K. "Endoscopic" adenoma detection rate as a quality indicator of colonoscopy: First report from the J-SCOUT study. *Dig Endosc.* 2023;35(5):615-24.
 30. Fukagawa K, Takahashi Y, Yamamichi N, Kageyama-Yahara N, Sakaguchi Y, Obata M, Cho R, Sakuma N, Nagao S, Miura Y, Tamura N, Ohki D, Mizutani H, Yakabi S, Minatsuki C, Niimi K, Tsuji Y, Yamamichi M, Shigi N, Tomida S, Abe H, Ushiku T, Koike K, Fujishiro M. Transcriptome analysis reveals the essential role of NK2 homeobox 1/thyroid transcription factor 1 (NKX2-1/TTF-1) in gastric adenocarcinoma of fundic-gland type. *Gastric Cancer.* 2023;26(1):44-54.

Pathology, Immunology and Microbiology

3. Immunology

Department of Immunology

Professor

Hiroshi Takayanagi, M.D., Ph.D.

Associate Professor

Takeshi Nitta, Ph.D.; Noriko Komatsu, Ph.D.

Assistant Professor

Hiroyuki Takaba, Ph.D.

Homepage <http://www.osteimmunology.com/>

Introduction and Organization

The history of the Department of Immunology can be traced back to its origins as the former Department of Serum Chemistry, established in 1918. The department adopted its present name when Dr. Tomio Tada took his position as professor and chair in 1977. Through his innovative research and great contributions to the international community of immunologists, he raised the stature of the department to a world-renowned status. After Dr. Tada's retirement in 1994, Dr. Tadatsugu Taniguchi (presently Emeritus Professor and Fellow of the Research Center for Advanced Science and Technology, the University of Tokyo) performed cutting-edge, internationally recognized research in the field of immunology, especially cytokine systems in the regulation of immunity and oncogenesis. His major achievements were the discovery of interferon- γ and a new family of transcription factors, termed interferon regulatory factors (IRFs). In May 2012, Dr. Hiroshi Takayanagi started the new laboratory aiming to shed light on two major questions: First, why is self-tolerance broken in autoimmune diseases? Second, what is the immune network among multiple organs, including bone and brain?

Teaching activities

All members of the department are deeply committed to teaching and mentoring the next generation of

scientists. Undergraduate students of the faculty take part in departmental class work through lectures on immunobiology, immunochemistry, and molecular immunology, as well as practical training by way of laboratory courses on basic immunology experimental techniques. The education of graduate students is based on weekly seminars where students present the progress of their own research projects, discuss the future directions of their research and the research of others, and are exposed to the latest cutting-edge questions confronting the research field of immunology. We also offer a special training course (called 'free quarter') of basic and advanced biological and immunological techniques to medical students. We are also accepting undergraduate students in the Medical Scientist Training Program in the faculty of medicine. In fiscal year 2022, special lectures for undergraduate students were given by internationally recognized scientists, Dr. Shimon Sakaguchi (Osaka University), Dr. Hiroshi Kawamoto (Kyoto University), and Dr. Tadatsugu Taniguchi (The University of Tokyo).

Research activities

We aim to achieve a further understanding of the mechanisms controlling the immune system, focusing on the development and function of tissue microenvironments in lymphoid organs, such as bone and thymus, and the molecular basis for lymphocyte development and activation. The final goal of our

study is to develop epoch-making strategies for the treatment of immune disorders such as autoimmune diseases and severe infectious diseases.

1) Osteoimmunology

The bone and immune systems share a variety of molecules and interact with each other under physiological and pathological conditions, constituting the “osteoimmune system,” which functions as a locomotor organ and a mineral reservoir as well as a primary lymphoid organ (Tsukasaki & Takayanagi. *Nat Rev Immunol.*, 2019).

The bone marrow is a primary lymphoid organ that plays a critical role in immune cell development. Osteoclasts are polynuclear cells derived from the monocyte/macrophage lineage, which are responsible for bone resorption. Aberrant osteoclast function and development is involved in the pathogenesis of several diseases such as the inflammatory bone destruction observed in rheumatoid arthritis as well as post-menopausal osteoporosis and osteopetrosis. Osteoclast development is dependent on the TNF family cytokine receptor activator of nuclear factor kappa-B ligand (RANKL). We studied the receptor signal transduction pathway for RANKL and identified NFATc1 as a master regulator for osteoclast differentiation (Takayanagi et al., *Dev Cell*, 2002; Asagiri et al., *J. Exp. Med.*, 2005). We also identified an ITAM-harboring co-receptor for RANK (Koga et al., *Nature*, 2004) and the importance of bridging signal cascade between RANK and ITAM via Btk for RANK-dependent osteoclastogenesis (Shinohara et al., *Cell*, 2008; Shinohara et al., *Bone*, 2014). Our recent proteomic analysis identified multiple target proteins phosphorylated upon differentiation of osteoclasts (Sumiya et al., *Biochem Biophys Res Commun.*, 2015).

Furthermore, we have revealed the roles of Semaphorin4D on osteoblast differentiation (Negishi-Koga et al., *Nature Med.*, 2011) and Semaphorin3A on inhibition of bone resorption as well as promotion of bone formation (Hayashi et al., *Nature*, 2012; Hayashi et al., *Cell Metab.*, 2019). We also found that immune complexes in serum activate osteoclastogenesis and cause bone loss through binding to Fcγ receptors (Negishi-Koga et al., *Nat Commun.*, 2015). To understand the precise mechanisms underlying cell

fate specification during osteoclast differentiation, we performed single-cell RNA sequencing analysis on the in vitro osteoclast culture system and provided a comprehensive picture of molecular processes underlying osteoclastogenesis (Tsukasaki et al., *Nat Metab.*, 2020, Tsukasaki et al., *Inflamm Regen.*, 2022).

The stromal cell types supporting hematopoietic cell development in the bone marrow have also been a focus of investigation. Osteoblasts play an essential role in maintaining common lymphoid progenitors through the production of IL-7. Genetic ablation of osteoblasts significantly reduced the number of common lymphoid progenitors in the bone marrow and peripheral mature lymphocytes (Terashima et al., *Immunity*, 2016). Further studies showed that acute inflammation, such as in sepsis, rapidly depletes osteoblasts, which leads to a reduction in common lymphoid progenitors and results in peripheral lymphopenia. This finding underscores the critical role of osteoblasts in the immune system and suggests their potential as therapeutic targets for treating inflammatory diseases.

Most recently, we found that oral bacteria promote the conversion of Foxp3⁺T cells into Th17 cells (exFoxp3Th17 cells) in periodontitis which is one of the most common infectious diseases. exFoxp3Th17 cells were found to be the most potent bone-damaging T cells. Interestingly, these bone-damaging exFoxp3Th17 cells protect against oral bacteria in two different ways. First, they elicit mucosal immune responses mainly by the production of anti-bacterial products. Second, they inhibit bacterial dissemination by removing the tooth. Thus, exFoxp3Th17 cells play a beneficial role in the host's defense against oral bacteria. This investigation highlighted the notion that T-cell-mediated bone damage, which was an adverse consequence of inflammation, may have developed to contribute to host defense against oral bacteria (Tsukasaki et al., *Nat Commun.*, 2018).

An anti-RANKL neutralizing antibody has been introduced for the treatment of osteoporosis, skeletal-related events by bone metastasis, and bone destruction in rheumatoid arthritis. We have demonstrated that oral administration of the novel small-molecule inhibitor against RANKL suppressed

bone metastasis using the mouse models, indicating the great efficacy of RANKL inhibition with a small-molecule compound in bone metastasis (Nakai et al., *Bone Res.*, 2019). RANKL is synthesized as a membrane-bound molecule and cleaved into its soluble form by proteases. We have reported that soluble RANKL is dispensable for the physiological regulation of bone and immune systems but has a distinct and pivotal role in the promotion of bone metastasis (Asano et al., *Nat Metab.*, 2019). The RANKL system plays a central role in bone and immune homeostasis, but the source of OPG, the decoy receptor for RANKL, has long been unknown. We generated OPG-floxed mice and showed that locally produced OPG, but not circulating OPG, has a crucial function in the thymus, bone, and intestine (Tsukasaki et al., *Cell Rep.*, 2020). The periosteum, a membranous tissue covering the outer surface of bones, has been considered to be involved only in intramembranous bone formation at the cortex. We revealed that stem cells residing in the periosteum control the homeostasis of the growth plate and bone marrow by secreting soluble factor *Ihh*, highlighting the importance of the periosteum as the key player in the osteoimmune system (Tsukasaki et al., *Nature Commun.*, 2022). These findings provided a new paradigm for the physiological interaction between bone and the immune system.

2) Lymphocyte development and lymphoid tissue microenvironment

The thymus is the primary lymphoid organ that supports the development of mature T cells (ex., positive and negative selection). We have focused on thymic fibroblasts, a stromal cell type with uncharacterized function in the thymus. Our results suggest that medullary fibroblasts may function in establishing self-tolerance by producing a unique set of self-antigens (Nitta et al., *Nat Immunol.*, 2020). Given the emerging recognition of fibroblasts for their functional diversity and regulatory roles across various organs through interactions with immune cells, our work provides valuable insights into their *in vivo* functions and their broader implications for immune regulation.

We have reported that the genetic variations of the human *PSMB11* gene, which encodes $\beta 5t$, a

thymus-specific proteasome subunit, affected the MHC class I-bound peptide repertoire in the thymus and positive selection of CD8 T cells (Nitta et al., *Sci Immunol.*, 2017). Among these variations, the G49S polymorphism, which occurs at a high frequency in the Japanese population, has been linked to an increased risk of Sjögren's syndrome. These findings suggest that, beyond the MHC haplotype, proteasome genetic variations play a critical role in shaping the T-cell repertoire and determining susceptibility to autoimmune diseases.

We have also been studying the thymic development of $\gamma\delta$ T cells. We showed that the $\gamma\delta$ TCR signal mediated by the Syk-PI3K pathway is essential for thymic development of IL-17-producing $\gamma\delta$ T cells (Muro et al., *J Clin Invest.*, 2018, Muro *Front Immunol.*, 2023). Recently, we have generated mutant mice lacking all of the *Skint* family genes (*Skint1-11*) that encode candidate thymic factors for regulation of $\gamma\delta$ T cell development (Narita et al., *Int Immunol.*, 2018). These mutant mice exhibited a significant reduction in V γ 5V δ 1 $\gamma\delta$ T cells in the thymus and skin, while other $\gamma\delta$ T cell subsets and leukocytes developed normally. This indicates a specific role for *Skint* family genes in V γ 5V δ 1 $\gamma\delta$ T cell development, providing an invaluable model for studying the mechanisms of thymic education in $\gamma\delta$ T cells. In addition, we explored the role of IL-17, a cytokine known to enhance osteoclastic bone resorption in pathological conditions. Using a mouse bone-fracture model, we demonstrated that IL-17 promotes bone fracture healing through osteoblastic bone formation. Furthermore, $\gamma\delta$ T cells were identified as the primary source of IL-17 at bone injury sites, underscoring their significant role in the bone healing process (Ono et al., *Nat Commun.*, 2016). These findings illuminate the dual roles of $\gamma\delta$ T cells in immune regulation and tissue repair.

Much attention has been paid to the development and function of the gut-associated lymphoid tissues (GALTs) and the symbiotic relationship between the gut microbiota and the host immune system. We identified a previously unrecognized subset of mesenchymal cells in the subepithelial dome of GALTs (Nagashima et al., *Nat Immunol.*, 2017). These cells expressed high levels of RANKL and directly interacted with the gut

epithelium to induce the microfold cell (M cell) differentiation and CCL20 expression. The deletion of RANKL in mesenchymal cells impaired M cell-dependent antigen sampling, which resulted in a reduction in IgA production and a decrease in microbial diversity, indicating that subepithelial RANKL-expressing mesenchymal cells (M cell inducer cells: MCi cells) are key players in the maintenance of host-microbe symbiosis. Furthermore, we reported that Col6a1-Cre driver mice are useful for studying the function of MCi cells (Nagashima et al., *Biochem Biophys Res Commun.*, 2017). Manipulation of MCi cells may provide a molecular basis for novel treatments of intestinal diseases such as inflammatory bowel disorders and infectious diseases.

We have recently found that protein arginine methylation, a post-translational modification, is an essential regulator of T-cell maintenance. T cell-specific deficiency of the arginine methyltransferase PRMT5 led to a decrease in the number of peripheral CD4, CD8, and regulatory T cells and an almost complete loss of iNKT cells. PRMT5-mediated arginine methylation was essential for the expression of the cytokine-signal-transducing components, the common cytokine receptor γ -chain (γ_c) and JAK3, which are required for the development of iNKT cells and the proliferation and survival of peripheral T cells. PRMT5 induced the arginine methylation of the spliceosomal component SmD3 that promoted the splicing of pre-mRNA encoding γ_c and JAK3. In recent years, Jak inhibitors have attracted attention as potential agents for autoimmune diseases such as rheumatoid arthritis. This study presented an entirely new regulatory mechanism governing γ_c family cytokine-Jak3 signaling in T cells (Inoue et al., *Nat Immunol.*, 2018).

3) Mechanism of autoimmune disease

The IL-17-producing helper T cell subset (Th17 cell) plays critical roles in several autoimmune disease models, such as collagen-induced arthritis (CIA) and experimental encephalomyelitis (EAE). We have identified I κ B ζ as an indispensable transcription factor for Th17 cell differentiation (Okamoto et al., *Nature*, 2010). However, in both RA and EAE models, the effector mechanisms of Th17 cells have been unclear. Recently, we identified a subset of Th17 cells that

robustly produces IL-17 and RANKL and exacerbates both inflammation and bone destruction in CIA mice. Interestingly, these Th17 cells are the progeny of CD4 T cells expressing Foxp3, a master regulator for immunosuppressive Treg cells (Komatsu et al., *Nat Med.*, 2014). We also reported that RANKL produced by synovial fibroblasts is primarily responsible for the formation of bone-destructive osteoclasts in inflammatory arthritis (Danks et al., *Ann Rheum Dis.*, 2016).

We identified that the transcription factor ETS1 is critical for the polarization of tissue-destructive synovial fibroblasts by upregulating both RANKL and MMP expression (Yan et al., *Nat Immunol.*, 2022). Periarticular bone loss is one of the earliest indices of RA, often preceding the onset of clinical symptoms via largely unknown mechanisms. We found that bone marrow plasma cells promote periarticular bone loss as RANKL-expressing osteoclast inducer cells (Komatsu et al., *J Clin Invest.*, 2021). These results, taken together, propose the importance of the immune-fibroblast-bone triad in autoimmune arthritis and suggest that targeting pathogenic cells and/or molecules could be effective in preventing bone destruction in RA (Komatsu and Takayanagi, *Nat Rev Rheumatol.*, 2022). We clarified that JAK inhibitors ameliorated bone erosion mainly by inhibiting osteoclast differentiation, while they ameliorate periarticular/systemic bone loss by both inhibiting osteoclasts and promoting osteoblasts (Komagamine et al., *Inflamm Regen.*, 2023). Under physiological conditions, we identified an osteocytic cell-specific enhancer region regulating RANKL expression. These suggest that bone absorption under the microenvironment is strictly regulated by cell type-specific RANKL enhancer regions (Yan et al. *Bone Res.*, 2023).

We have also been focusing on neuro-autoimmune diseases, and in recent years, we discovered that in mouse models of multiple sclerosis (experimental autoimmune encephalomyelitis: EAE), T cells in the central nervous system act on astrocytes via RANKL, promoting the infiltration of numerous immune cells and causing chronic inflammation. Furthermore, we found that the administration of a small molecule inhibitor of RANKL suppresses the onset of EAE, presenting a new potential treatment for multiple sclerosis (Guerrini et al., *Immunity*, 2015).

We have also been studying the mechanism of T cell-mediated self-tolerance induction because a breakdown of T cell tolerance induces autoimmune diseases. Self-tolerance of T cells is primarily established during their development in the thymic medulla, where medullary thymic epithelial cells (mTECs) ectopically express a variety of tissue-restricted antigens (TRAs) and thereby TRA-reactive immature T cells are deleted. It has been known that the expression of a set of TRAs is regulated by the transcriptional regulator Aire, although how the remaining TRAs are regulated has been unclear. We identified a novel key transcription factor, Fezf2, which is highly expressed in mTECs and controls the expression of a large fraction of Aire-independent TRAs (Takaba et al., *Cell*, 2015). Mice lacking Fezf2 in mTECs exhibited severe autoimmune disorders in peripheral organs, and the spectrum of autoimmunity in Fezf2-deficient mice differed from that in Aire-deficient mice. These results indicate that two independent factors, Fezf2 and Aire, play non-redundant and mutually complementary roles in the TRA expression to ensure T cell tolerance induction. In addition, we identified a chromatin remodeler, Chd4, interacting with Fezf2. Chd4 works with not only Fezf2 but also Aire to promote promiscuous TRA expression in mTECs, mediating central immune tolerance (Tomofuji et al., *Nat Immunol.*, 2020). We also reported that the transcription factor Sox4 is required for the development of thymic tuft cells, a subset of terminally differentiated mTECs (Mino et al., *Int Immunol.*, 2022), suggesting that these cells utilize transcriptional programs akin to peripheral epithelial cells, effectively projecting an immunological self within the thymus to reinforce central tolerance. Collectively, these findings provide significant insights into the molecular mechanisms driving autoimmune disease and immune tolerance. By elucidating the interplay between immune cells, fibroblasts, and bone regulation, as well as the thymic pathways underpinning T-cell tolerance, our work underscores novel therapeutic targets for preventing inflammation, bone destruction, and autoimmunity.

References

1. Nitta et al., Fibroblasts as a source of self-antigens for central immune tolerance. *Nat Immunol.*, 21: 1172–1180. (2020)
2. Muro et al., Spleen tyrosine kinase mediates the $\gamma\delta$ TCR signaling required for $\gamma\delta$ T cell commitment and $\gamma\delta$ T17 differentiation. *Front Immunol.*, 13:1045881 (2023)
3. Yan M et al., ETS1 governs pathological tissue-remodeling programs in disease-associated fibroblasts. *Nat Immunol.* 23(9):1330-1341. (2022)
4. Komatsu et al., Plasma cells promote osteoclastogenesis and periarticular bone loss in autoimmune arthritis. *J Clin Invest.*, 131: e143060. (2021)
5. Komagamine et al., Effect of JAK inhibitors on the three forms of bone damage in autoimmune arthritis: joint erosion, periarticular osteopenia, and systemic bone loss. *Inflamm Regen.*, 43:44 (2023)
6. Yan M et al., Identification of an intronic enhancer regulating RANKL expression in osteocytic cells. *Bone Res.* 11:43 (2023).
7. Komatsu N and Takayanagi H Mechanisms of joint destruction in rheumatoid arthritis —immune system—fibroblast—bone interactions *Nat Rev Rheumatol.* 18(7):415-429. (2022)
8. Tsukasaki et al., Periosteal stem cells control growth plate stem cells during postnatal skeletal growth. *Nature Communications* 13:4166. (2022)
9. Tomofuji et al., Chd4 choreographs self-antigen expression for central immune tolerance. *Nat Immunol.*, 21: 892–901. (2020)
10. Mino et al., The Transcription Factor Sox4 is Required for Thymic Tuft Cell Development. *Int Immunol.*, 34: 45-52. (2022)

Radiology and Biomedical Engineering

1. Radiology

Department of Radiology

Professor

Osamu Abe, M.D., Ph.D.

Associate Professor

Hideomi Yamashita, M.D., Ph.D., Hidemasa Takao, M.D., Ph.D.,
Takeyuki Watadani, M.D., Ph.D.

Lecturer

Shouhei Hanaoka, M.D., Ph.D., Shiori Amemiya, M.D., Ph.D., Atsuto Katano, M.D., Ph.D.

Project Lecturer

Mami Ogita, M.D., Ph.D., Eisuke Shibata, M.D., Ph.D.

Assistant Professor

Kanabu Nawa, Ph.D., Koichiro Yasaka, M.D., Ph.D., Yusuke Watanabe, M.D., Ph.D., Yudai Nakai, M.D., Ph.D., Takatoshi Kubo, M.D., Ph.D., Ryo Kurokawa, M.D., Ph.D., Masafumi Kaiume, M.D., Ph.D., Subaru Sawayanagi, M.D., Yosuke Miki, M.D., Ph.D.

Project Assistant Professor

Shohei Inui, M.D., Ph.D., Saori Koshino, M.D., Takeshi Ohta, R.T., Ph.D., Hisaichi Shibata, Ph.D., Tomomi Takenaga, R.T., Ph.D., Yuki Nozawa, M.Sc.

Homepage <http://www.ut-radiology.umin.jp/>

Introduction and Organization

Department of Radiology was established in 1932. Radiology covers three major fields that are, Diagnostic Radiology (imaging and intervention), Radiation Oncology (radiotherapy), and Nuclear Medicine. The clinical, educational and research activities of our department are being carried out in cooperation with Department of Radiology in The Research Institute of Medical Science, which has three (1 associate professor, 1 lecturer, and 2 assistant professor) positions. In addition, Department of Radiology mainly takes care of radiation protection and radiation safety in the hospital.

Clinical activities

Clinical services on Diagnostic Radiology, Nuclear

Medicine, and Radiation Oncology are provided in the Radiology Center in cooperation with radiology technologists and nurses.

In the section of Diagnostic Radiology, all CT and MRI examinations are monitored and reported by diagnostic radiologists. Diagnostic radiologists, gastroenterologists, cardiologists, and neurosurgeons mainly perform interventional procedures.

In the section of Nuclear Medicine, two cyclotrons and several remote or processor-controlled automated devices are installed, which facilitate standardized procedures in the PET tracer production and the implementation of GMP in PET-related work. There are two SPECT rooms and two PET rooms. These nuclear imaging procedures are chiefly performed and reported by diagnostic radiologists and cardiologists.

Each year, over 700 new patients receive radiation therapy in the Radiation Oncology section. Highly accurate 3D radiation therapy is the most outstanding feature. Stereotactic radiation therapy for small lung or liver tumors has been carried out.

In the 9th floor of the Inpatient Building A, there are 12 beds in the Radiology ward, which are usually used for oncology patients receiving radiation therapy and chemotherapy. Some of them are sometimes used for patients receiving invasive diagnostic procedures such as interventional radiology (IVR), angiography and myelography. There are two special beds for radionuclide (RN) therapy in the same floor. In addition, four beds are allotted to terminal care ward located in the 14th floor.

Education

Lectures are given to the fourth-, fifth- and sixth-year students to provide fundamental knowledge of diagnostic radiology, radiation oncology, and nuclear medicine. Professor, associate professors and lecturers as well as specialists assigned as part time lecturers take part in the education. A series of lectures about fundamentals of radiology and related sciences are given to the fourth-year students. As bed-side-learning (Clinical Clerkship, CC) curriculum, small groups of the sixth-year students are taking part in mini-lectures and practice to learn basics of diagnostic radiology, advanced medical techniques of Radiation Oncology and Nuclear Medicine. They will learn detailed principles of image constructions in various kinds of imaging modalities and technology in radiation therapy against cancer. Postgraduate students are also welcome to each of subspecialties of radiology according to their interests.

Research

Research activities in our department include clinical research, animal experiments, and development of instruments as well as computer-based new technology including artificial intelligence. Diagnostic Radiology group in the department promotes research activities aiming at efficacy improvement of diagnostic imaging and expansion of its application. Multi-row detector helical computed tomography (MDCT) enables us to take tomographic

images in a three- or four-dimensional (3D, 4D) fashion. Using the data acquired by MDCT, various kinds of diseases in almost all parts of the body, from cerebral to musculoskeletal diseases, can be displayed in 3D or time-resolved 3D images. New 3D software developed in our departments is now widely used in the field of the gastrointestinal tract, lung, and central nervous system. In addition, we have opened a new laboratory section named Image Computing and Analysis Laboratory with invitation of experts of engineering. This section will contribute to development of novel software including convolutional neural network to abstract clinically useful information from the 3D imaging data more sophisticatedly. In the field of magnetic resonance (MR) imaging, structural and functional MRI, perfusion and diffusion imaging are the researches of interest. These techniques are aggressively applied to the investigation of vascular and neoplastic diseases of the brain.

Radiation oncology group promotes research projects in two major fields; one is physical engineering such as the optimization of dose distribution in the radiation therapy (RT) and the other is reduction of injuries due to radiation exposure in vitro and in vivo. This group pushes forward studies mainly on a brain tumor, head and neck cancer, esophageal cancer, uterine cervical cancer, prostate cancer in conformity with recent EBM in the clinical study, and is active in studies of the physical engineering traditionally and plays a main role in the highly precise radiation therapy of our country until now. With the purpose of achieving precise external irradiation, a new linear accelerator with multileaf collimator systems was developed and installed, which is utilized mainly for non-coplanar radiation therapy in many patients, especially with brain tumor or head and neck tumor. Dynamic conical conformal radiotherapy for metastatic brain tumors using the accelerator is under evaluation. In addition to gamma knife radiosurgery, this new accelerator based stereotactic radiotherapy for brain diseases has been undergone, and stereotactic radiotherapy (SRT) for body tumors, such as head and neck cancer, prostate cancer, rectal cancer and lung cancer, has been investigated in combination with intensity modulation radiation therapy (IMRT) for the reduction of the

adverse radiation damage. A new technology to track mobile tumors, represented by lung tumors, is under investigation in collaboration with accelerator makers.

Nuclear Medicine group promotes clinical research on functional imaging by the application of radioisotope-labeled tracer technology, combined with molecular biology. In particular, emission tomography (PET and SPECT) is applied for the evaluation of cerebral blood flow and metabolism in patients with dementia, epilepsy, and cerebrovascular diseases. Cerebral blood flow, glucose metabolism, and neural synaptic functions are measured for the understanding of normal and pathophysiological states of CNS disorders, using a variety of positron-emitter radiotracer, such as [F-18] FDG,. The study of dementia using SPECT and the standard brain atlas has made it possible to categorize the type of dementia. Evaluation of dopaminergic function by SPECT is very important in the differential diagnosis of Parkinsonism. Cardiac PET and SPECT are also active fields. Myocardial viability, vascular reserve, and sympathetic nerve denervation in the ischemic heart disease are evaluated with [F-18] FDG, Tl-201 and [I-123] MIBG. Higher brain functions such as reading, speech, and thinking have been studied with PET by comparing blood flow and receptor binding potential (BP) under various tasks and at rest. For the precise localization of activated brain function, computer processing and reconstruction of composite images of function and anatomy is an essential subject for investigation. At present, whole body FDG-PET is one of the most effective tool for exploring metastatic lesions of cancer patients. Combination display of SPECT/PET with CT/MRI would be a routine job and anatomo-functional images would play an important role in the clinical management of the patients.

Conclusion

Diagnostic radiology, radiotherapy and nuclear medicine are the three pillars that support radiology. Mutual cooperation among these three fields, which are divided by modality, is the basis for comprehensive diagnostic imaging and multi-disciplinary treatment, and our department has been working vigorously toward its realization. In the future, there is a strong need to train more field-

oriented radiologists who have cross-cutting knowledge, experience, and research achievements in each field.

Publications

One hundred and forty-three, 126, and 137 English original articles have been published from our department in 2023, 2022, and 2021. respectively. Please refer to our homepage, <http://www.ut-radiology.umin.jp/publication/2023.html>.

Radiology and Biomedical Engineering

2. Biomedical Engineering

Department of System Physiology

Professor (Concurrent)

Kiyoshi Miyagawa, M.D., Ph.D.

Associate Professor

Kimiko Yamamoto, M.D., Ph.D.

※The following information is the same as that of the previous year for certain reasons.

Homepage https://square.umin.ac.jp/bme/research_Eng.html

Introduction and Organization

Our department originated from the department of Basic Medical Science, the Institute of Medical Electronics, established in 1961. In 1997, as a result of the shift to the chair system of the Graduate School of Medicine, the Institute was replaced with three departments of Biomedical Engineering: System Physiology, Bioimaging and Biomagnetics, and Biosystem Construction and Control. The Department of System Physiology consists of a Professor (concurrent) and an Associate Professor.

Teaching activities

We give lectures of “Early Exposure to Medicine” for first year students, “Basic Principles of Biomedical Engineering” for second and third year students, “Introduction to Biomedical Engineering” for postgraduate students, “Introduction to Medical Science: Mechanobiology” for master’s students, in the faculty of Medicine, and “Principles of Medicine” for postgraduate students in the faculty of Engineering. We offer practical training of biomedical engineering research to third- and fourth-year students of undergraduate medical school. A weekly seminar is held in our laboratory bringing together staff and research fellows to discuss journal articles and give updates on experiments. Our aim is to enhance the research skills of students.

Research activities

This laboratory has been pursuing the study of biomechanics dealing with mechanical phenomena in the human body, especially focusing on cellular sensing and response mechanisms to mechanical stimuli. The main theme of our work is the relationships between shear stress or cyclic strain, which are hemodynamic forces generated by blood flow, and their target cells, vascular endothelial cells (ECs). This would be of benefit not only to understanding blood flow-mediated regulation of vascular functions but also to the elucidation of clinically important problems such as angiogenesis, vascular remodeling, atherogenesis, and development of cerebral aneurysm which occur in a blood flow-dependent manner.

Original biomedical engineering methods have been applied, in which cultured ECs are exposed to controlled levels of shear stress or cyclic strain in a fluid–dynamic flow apparatus and whose responses are analyzed at the cellular and molecular levels. Microcirculatory hemodynamics and oxygen transport of genetically modified mice are studied by employing opto-electronics technology. The results of these experiments are listed below.

1. Cell responses to hemodynamic forces
2. Hemodynamic force-mediated gene regulation
3. Hemodynamic force-induced cell differentiation
4. Mechanosensing and mechanotransduction
5. Shear stress-induced mitochondria oxidative Phosphorylation

6. Hemodynamic force-induced changes in plasma membrane cholesterol levels

1. Cell responses to hemodynamic forces

Our studies have demonstrated that ECs have functional responses to hemodynamic forces, shear stress and cyclic strain. When a cultured EC monolayer was partially denuded, surrounding cells migrated and proliferated in the denuded area, and covered the denuded area. Shear stress enhanced the regenerative functions of ECs. Shear stress increased the production of nitric oxide, a potent vasodilator, in ECs in a dose-dependent manner. Shear stress also increased the expression of thrombomodulin, an antithrombotic molecule, in ECs. In contrast, it decreased the expression of vascular cell adhesion, which leads to the inhibition of leukocyte adhesion to vascular cell adhesion molecule-1 (VCAM-1). It was shown that shear stress increases the levels of adrenomedullin and C-type natriuretic peptide mRNA which have vasodilating effects in addition to nitric oxide, and that it also augmented the expression of lectin like low density lipoprotein receptor (LOX-1) at the protein and mRNA level.

2. Hemodynamic force-mediated gene regulation

We have demonstrated that shear stress regulates endothelial gene expression transcriptionally and/or posttranscriptionally. Shear stress downregulates VCAM-1 gene transcription via the double AP-1 binding element (TGACTCA) in the promoter which functions as a shear stress-responsive element. Shear stress has also been shown to increase the expression level of granulocyte/macrophage-colony stimulating factor (GM-CSF) via mRNA stabilization. Differential display and DNA microarray analysis showed that around 600 known and unknown transcripts were up- or down-regulated in human umbilical vein ECs exposed to a shear stress. From these shear stress-responsive genes, a cDNA encoding an unknown G-protein coupled receptor was cloned. We showed that the transcription factor SP1 is involved in the shear stress-induced down-regulation of P2X4 (an ATP-gated cation channel) gene expression in ECs. We also revealed that endothelial genes are differentially regulated by laminar and turbulent shear stress. Laminar shear stress decreases the gene expression of

urokinase plasminogen activator (uPA), which plays a role in fibrinolysis and vascular remodeling, via both GATA6-mediated down-regulation of gene transcription and an acceleration of mRNA degradation, while turbulent shear stress increases the uPA gene expression through mRNA stabilization. We demonstrated that shear stress up-regulates the gene expression of plasminogen activator inhibitor-1 (PAI-1) through activation of transcription factors Sp-1 and Ets-1 in human hepatocytes. We developed a compliant tube-type flow-loading device that allows simultaneous application of physiological levels of shear stress and cyclic strain to cultured cells and observed that the response of endothelial genes to shear stress or cyclic strain depends on whether the two forces are applied separately or together.

3. Hemodynamic force-induced cell differentiation

We have revealed that endothelial progenitor cells (EPCs) circulating in human peripheral blood proliferate and differentiate into mature ECs in response to shear stress, thereby forming tube-like structures in collagen gel. Moreover, we revealed that shear stress increased the gene expression of the arterial EC marker ephrinB2 in EPCs, while it decreased the gene expression of the venous EC marker EphB4, suggesting that shear stress affects arterial-venous differentiation of EPCs.

Embryonic stem (ES) cells have the potential to differentiate into every cell type in the body, and attracting interest as a promising source of cells for use in regenerative medicine. Embryonic cells are exposed to fluid-mechanical forces, including shear stress and the cyclic strain generated by beating heart during the process of embryonic development. We found that shear stress induces the differentiation of murine ES cells into vascular EC lineage in vitro; cyclic strain induces the differentiation into vascular smooth muscle cell (SMC) lineage. Differentiation into the EC lineage and differentiation into SMC lineage are mediated by ligand-independent phosphorylation of vascular endothelial growth factor receptor 2 (VEGFR2) and platelet derived growth factor receptor (PDGFR), respectively. Moreover, our study has shown that shear stress increases expression of ephrinB2 in murine ES cells via the VEGF-Notch signaling pathways, suggesting that shear stress can also affect the arterial-

venous differentiation of ES cells. Based on these findings, in a collaborative study, a new hybrid type of artificial blood vessel, in which ES cells were cultured on the surface of polymer tubes and exposed to pulsatile shear stress and cyclic strain, was developed.

4. Mechanosensing and mechanotransduction

We were the first to show that Ca^{2+} signaling plays an important role in the mechanism by which ECs recognize the shear stress signal and transmit it into the cell interior. Strong shearing forces induced by dragging ECs with a balloon causes an increase in cytoplasmic Ca^{2+} concentrations. A relatively weak shearing force like shear stress generated by fluid flow needs the presence of extracellular ATP to induce Ca^{2+} response, and at several hundred nanomolar of ATP, intracellular Ca^{2+} concentrations increase in a shear stress-dependent manner. Generally, flow-induced Ca^{2+} responses are initiated at a locus at the cell edge and propagate throughout the entire cell in the form of a Ca^{2+} wave. The initiation locus corresponded precisely to caveolae rich cell edges. We found that a subtype of ATP-gated cation channel, the P2X4 receptor, is expressed in human vascular ECs and that P2X4 receptors play a crucial role in the shear stress-dependent Ca^{2+} response. Endogenously released ATP by shear stress is involved in the P2X4-mediated Ca^{2+} responses. We produced *P2X4*-deficient mice and observed that the P2X4-deficient mice have impaired flow-dependent control of vascular tone and remodeling, indicating that shear stress signal transduction via P2X4 plays a critical role in the regulation of circulatory functions.

Our study revealed that cell surface ATP synthase localized in caveolae/lipid rafts are involved in the shear-stress-induced ATP release by ECs. Recently, we demonstrate that the cellular mitochondria play a critical role in this process. Cultured human pulmonary artery ECs were exposed to controlled levels of shear stress in a flow-loading device and the changes in the mitochondrial ATP levels were examined by real-time imaging using a fluorescence resonance energy transfer-based ATP biosensor. Immediately upon the exposure of the cells to flow, the mitochondrial ATP levels increased, which was both reversible and dependent on the shear stress intensity. Inhibitors of the mitochondrial electron transport chain and ATP

synthase, as well as knockdown of caveolin-1, a major structural protein of the caveolae, abolished the shear-stress-induced mitochondrial ATP generation, resulting in the loss of the ATP release and influx of Ca^{2+} into the cells. These results suggest the novel role of the mitochondria in transducing the shear stress into ATP generation: the ATP generation leads to ATP release in the caveolae, triggering purinergic Ca^{2+} signaling. Thus, exposure of ECs to shear stress seems to activate mitochondrial ATP generation through caveola- or caveolin-1- mediated mechanisms.

Moreover, we report that the plasma membrane itself differentiates between shear stress and stretch by undergoing transitions in its lipid phases. Shear stress decreased the lipid order of human pulmonary artery EC plasma membranes, thereby causing a transition from the liquid-ordered phase to the liquid-disordered phase in some areas, along with an increase in membrane fluidity. In contrast, uniaxial stretching and hypotonic swelling increased the membrane lipid order and decreased membrane fluidity. A similar increase in lipid order occurred when the artificial lipid bilayer membranes of giant unilamellar vesicles were stimulated by shear stress by using a flow-loading apparatus or stretched by hypotonic swelling, indicating that mechanical force-mediated responses of lipid membranes are physical phenomena. The cholesterol content of EC plasma membranes significantly decreased in response to shear stress but clearly increased in response to stretch. Blocking these changes in the membrane lipid order by depleting membrane cholesterol with methyl- β -cyclodextrin or by adding cholesterol resulted in a marked inhibition of the EC response specific to shear stress and stretch, i.e., phosphorylation of VEGFR2 and phosphorylation of PDGFR, respectively. These findings indicate that EC plasma membranes differently respond to shear stress and stretch by changing their lipid order, fluidity, and cholesterol content in opposite directions and that these changes in membrane physical properties are involved in the mechanosensing mechanisms and the mechanotransduction that activates membrane receptors specific to each force.

5. Shear stress-induced mitochondria oxidative phosphorylation

Vascular endothelial cells (ECs) sense and

respond to hemodynamic shear stress, which is critical for circulatory homeostasis and the pathophysiology of vascular diseases. The mechanisms of shear stress mechanotransduction, however, remain elusive. We previously demonstrated a direct role of mitochondria in the purinergic signaling of shear stress: shear stress increases mitochondrial ATP production, triggering ATP release and Ca^{2+} signaling via EC purinoceptors. Here, we showed that shear stress rapidly decreases cholesterol in the plasma membrane, thereby activating mitochondrial ATP production. Imaging using D4 mutant-derived cholesterol biosensors showed that the application of shear stress to cultured ECs markedly decreased cholesterol levels in both the outer and inner plasma membrane bilayers. Flow cytometry showed that the cholesterol levels in the outer bilayer began to decrease within 3 min after the onset of shear stress, reached a minimum (around 60% of the control level) at 10 min, and plateaued thereafter. After the shear stress ceased, the decreased cholesterol levels returned to those seen in the control. A biochemical analysis showed that shear stress caused both the efflux and the internalization of plasma membrane cholesterol. ATP biosensor imaging demonstrated that shear stress significantly increased mitochondrial ATP production. Similarly, the treatment of cells with methyl- β -cyclodextrin (M β CD), a membrane-cholesterol-depleting agent, increased mitochondrial ATP production. The addition of cholesterol to cells inhibited the increasing effects of both shear stress and M β CD on mitochondrial ATP production in a dose-dependent manner. These findings indicate that plasma membrane cholesterol dynamics are closely coupled to mitochondrial oxidative phosphorylation in ECs.

6. Hemodynamic force-induced changes in plasma membrane cholesterol levels

Vascular endothelial cells (ECs) sense and respond to hemodynamic shear stress, which is critical for circulatory homeostasis and the pathophysiology of vascular diseases. The mechanisms of shear stress mechanotransduction, however, remain elusive. We previously demonstrated a direct role of mitochondria in the purinergic signaling of shear stress: shear

stress increases mitochondrial ATP production, triggering ATP release and Ca^{2+} signaling via EC purinoceptors. Here, we showed that shear stress rapidly decreases cholesterol in the plasma membrane, thereby activating mitochondrial ATP production. Imaging using D4 mutant-derived cholesterol biosensors showed that the application of shear stress to cultured ECs markedly decreased cholesterol levels in both the outer and inner plasma membrane bilayers. Flow cytometry showed that the cholesterol levels in the outer bilayer decreased rapidly after the onset of shear stress, reached a minimum (around 60% of the control level) at 10 min, and plateaued thereafter. After the shear stress ceased, the decreased cholesterol levels returned to those seen in the control. A biochemical analysis showed that shear stress caused both the efflux and the internalization of plasma membrane cholesterol. ATP biosensor imaging demonstrated that shear stress significantly increased mitochondrial ATP production. Similarly, the treatment of cells with methyl- β -cyclodextrin (M β CD), a membrane-cholesterol-depleting agent, increased mitochondrial ATP production. The addition of cholesterol to cells inhibited the increasing effects of both shear stress and M β CD on mitochondrial ATP production in a dose-dependent manner. These findings indicate that plasma membrane cholesterol dynamics are closely coupled to mitochondrial oxidative phosphorylation in ECs.

References

1. J. Ando and K. Yamamoto. Hemodynamic forces, endothelial mechanotransduction, and vascular diseases. *Magn. Reson. Med. Sci.*, 21(2), 258-266 (2022).
2. I. Ono, Y. Abekura, A. Kawashima, M. Oka, A. Okada, S. Hara, S. Miyamoto, H. Kataoka, A. Ishii, K. Yamamoto, T. Aoki, Endothelial Cell Malfunction in Unruptured Intracranial Aneurysm Lesions Revealed Using a 3D-Casted Mold, *J. Neuropathol. Exp. Neurol.* 82(1), 49-56 (2022).
3. K. Yoshida, S. Tanihara, Y. Miyashita, K. Obayashi, M. Ito, K. Yamamoto, T. Imai, and I. Matsuoka, P2X4 receptor stimulation enhances MrgprB2-mediated mast cell activation and pseudoallergic reactions in mice. *Sci. Rep.*, 12, Article

number: 18613 (2022).

4. K. Obayashi, K. Yoshida, M. Ito, T. Mori, K. Yamamoto, T. Imai, I. Matsuoka, Synergistic cytokine production by ATP and PGE2 via P2X4 and EP3 receptors in mouse bone marrow-derived mast cells. *Cells*. 11 (4), 616 (2022).

Department of Chemical Biology and Molecular Imaging

Professor

Yasuteru Urano, Ph.D.

Associate Professor

Ryosuke Kojima, Ph.D.

Assistant Professor

Kyohhei Fujita, Ph.D.

Webpage <http://cbmi.m.u-tokyo.ac.jp/>

Introduction and Organization

The Laboratory of Chemical Biology and Molecular Imaging is one of the laboratories in the department of Radiology and Biomedical Engineering. Our laboratory is located in the annex of the medical building 3. Our lab members consist of 3 postdoctoral researcher, 7 PhD students, 5 master course students, 1 undergraduate student, and 2 guest researchers, as of FY2023.

Teaching activities

As for under-graduate education, our laboratory takes part in medical engineering lectures for the 3rd year medical students. As for PhD course education, our laboratory delivers the lecture of fluorescence imaging for both master and doctor course students.

Research activities

In our laboratory, we conduct research aimed at developing various fluorescence imaging probes and their biological and medical applications. In fiscal year 2023, we reported on the development of fluorescence probe for cholangiocarcinoma in the Extrahepatic Biliary Tree, calboxypeptidase-reactive fluorescence probe based on ProTide Chemistry, and super-resolution vibrational imaging based on

photoswitchable Raman probe etc. Details are as follows.

The treatment of extrahepatic cholangiocarcinoma (eCCA) is only possible through complete resection. However, with current imaging techniques, it remains challenging to accurately diagnose the longitudinal extent of the cancer. This study aimed to develop a fluorescence imaging technique to identify eCCA in real time using enzyme-activated detection probes that emit fluorescence upon activation by cancer-specific enzymes. Using lysates and small tissue samples collected from surgically resected specimens, we selected the most specific probe for eCCA from 800 probes. The selected probe was sprayed directly onto resected specimens, and fluorescence images were obtained to evaluate diagnostic accuracy. Additionally, the target enzyme of the probe was comprehensively investigated, and the expression levels of this enzyme in cancerous and non-cancerous tissues were compared. Analysis of 19 samples (4 cancer lysates, 7 non-cancer lysates, and 8 bile samples) and 54 tissue fragments (13 cancerous tissues and 41 non-cancerous tissues) revealed that PM-2MeSiR was the most specific fluorescent probe for eCCA. Fluorescence imaging from 7 patients enabled rapid identification of cancerous areas, and the results closely correlated with histopathological findings in 4 of these patients. Puromycin-sensitive aminopeptidase was identified as

the target enzyme of the probe, and its expression was found to be elevated in eCCA. Fluorescence imaging diagnosis using PM-2MeSiR targeting puromycin-sensitive aminopeptidase demonstrated generally high accuracy. This technique shows potential for real-time identification of eCCA spread during surgery or endoscopic procedures. (Publication 1)

Carboxypeptidases (CPs) are a family of hydrolase enzymes that cleave one or more amino acids from the C-terminus of peptides and proteins, playing essential roles in various physiological and pathological processes. However, only a limited number of fluorescent probes for detecting CP activity have been reported. This has highlighted the need for the development of a molecular design platform that provides diverse fluorescent probes targeting CPs for biological and medical research. In this study, we established a modular design platform for CP activity-detecting fluorescent probes based on ProTide chemistry. This design platform allows for the facile adjustment and optimization of probe characteristics, such as fluorescence wavelength, reactivity/stability, and target CP specificity, by modifying four probe modules: the fluorophore, the substituent on the phosphorus atom, the linker amino acid at the P1 position, and the substrate amino acid at the P1' position. Notably, we found that changing the linker amino acid at the P1 position enabled precise optimization of reactivity toward specific target CPs. As proof of concept, we developed probes targeting Carboxypeptidase M (CPM) and Prostate-Specific Membrane Antigen (PSMA). These probes were confirmed to be applicable for imaging CP activity in live cells and patient-derived clinical specimens. This design strategy is anticipated to be a valuable tool for studying CP-related biological and pathological phenomena. (Publication 2)

Super-resolution vibrational microscopy is a promising technology for enhancing the degree of multiplexing in nanoscale biological imaging, owing to the narrower spectral linewidth of molecular vibrations compared to fluorescence. However, current super-resolution vibrational microscopy techniques face various limitations, such as the need for cell fixation, high power loads, or complex detection schemes. In this study, we proposed Reversible Saturated Optical Raman Transition

(RESORT) microscopy to overcome these limitations by utilizing stimulated Raman scattering (SRS). First, we developed a high-brightness visible-excitation Raman probe (DAE620) and validated its signal activation and erasure properties under low-power continuous-wave laser illumination. Next, by employing a donut-shaped beam to erase the SRS signal of DAE620, we achieved super-resolution vibrational imaging of mammalian cells with excellent chemical specificity and spatial resolution beyond the optical diffraction limit. These results demonstrate that RESORT microscopy is an effective tool with significant potential for multiplexed super-resolution imaging of live cells. (Publication 3).

Additionally, we have conducted and published several collaborative research projects with researchers both within and outside the university (Publications 4-8).

References

- (1) Takahashi, R.; Ishizawa, T.; Inagaki, Y.; Tanaka, M.; Ogasawara, A.; Kuriki, Y.; Fujita, K.; Kamiya, M.; Ushiku, T.; Urano, Y.; et al. Real-Time Fluorescence Imaging to Identify Cholangiocarcinoma in the Extrahepatic Biliary Tree Using an Enzyme-Activatable Probe. *Liver Cancer* **2023**, 1-13. DOI: 10.1159/000530645.
- (2) Kuriki, Y.; Sogawa, M.; Komatsu, T.; Kawatani, M.; Fujioka, H.; Fujita, K.; Ueno, T.; Hanaoka, K.; Kojima, R.; Hino, R.; et al. Modular Design Platform for Activatable Fluorescence Probes Targeting Carboxypeptidases Based on ProTide Chemistry. *Journal of the American Chemical Society* **2023**. DOI: 10.1021/jacs.3c10086.
- (3) Shou, J.; Komazawa, A.; Wachi, Y.; Kawatani, M.; Fujioka, H.; Spratt, S. J.; Mizuguchi, T.; Oguchi, K.; Akaboshi, H.; Obata, F.; et al. Super-resolution vibrational imaging based on photoswitchable Raman probe. *Sci Adv* **2023**, 9 (24), eade9118. DOI: 10.1126/sciadv.ade9118.
- (4) Tanaka, K.; Tanigawa, N.; Song, I.; Komatsu, T.; Kuriki, Y.; Tanaka, Y.; Fukudo, S.; Urano, Y.; Fukuda, S. A protease activity-based machine-learning approach as a complementary tool for conventional diagnosis of diarrhea-predominant irritable bowel syndrome. *Frontiers in*

microbiology **2023**, *14*, 1179534. DOI: 10.3389/fmicb.2023.1179534.

- (5) Iriki, T.; Iio, H.; Yasuda, S.; Masuta, S.; Kato, M.; Kosako, H.; Hirayama, S.; Endo, A.; Ohtake, F.; Kamiya, M.; et al. Senescent cells form nuclear foci that contain the 26S proteasome. *Cell reports* **2023**, *42* (8), 112880. DOI: 10.1016/j.celrep.2023.112880.
- (6) Echizen, H.; Hanaoka, K.; Shimamoto, K.; Hibi, R.; Toma-Fukai, S.; Ohno, H.; Sasaki, E.; Komatsu, T.; Ueno, T.; Tsuchiya, Y.; et al. Discovery of a cystathionine γ -lyase (CSE)selective inhibitor targeting active-site pyridoxal 5'-phosphate (PLP) via Schiff base formation. *Sci Rep* **2023**, *13* (1), 16456. DOI: 10.1038/s41598-023-43536-6.
- (7) Tsuchimochi, S.; Wada-Hiraike, O.; Urano, Y.; Kukita, A.; Yamaguchi, K.; Honjo, H.; Taguchi, A.; Tanikawa, M.; Sone, K.; Mori-Uchino, M.; et al. Characterization of a fluorescence imaging probe that exploits metabolic dependency of ovarian clear cell carcinoma. *Sci Rep* **2023**, *13* (1), 20292. DOI: 10.1038/s41598-023-47637-0.
- (8) Ishizawa, T.; Kuriki, Y.; Kamiya, M.; Ichida, A.; Kawaguchi, Y.; Akamatsu, N.; Kaneko, J.; Arita, J.; Kokudo, N.; et al. Evaluation of pancreatic chymotrypsin activity for on-site prediction of clinically relevant postoperative pancreatic fistula. *Pancreatology : official journal of the International Association of Pancreatology (IAP) ... [et al.]* **2024**, *24* (1), 169-177. DOI: 10.1016/j.pan.2023.11.017.

Division of Integrative Genomics

Professor

Katsutoshi Oda, M.D., Ph.D.

Associate Professor

Aya Ushiku, M.D., Ph.D.

Organization

The division of Integrative Genomics was established in January 2020 to comprehensively promote genomic research both clinically and basically. The activity of this division is linked to the Department of Clinical Genomics and Genomic Research Support Center, as well as the Department of Next-Generation Precision Medicine Development Laboratory. We focus on both basic research and translational research in the field of genomics (especially genomic medicine in cancer).

Activities

Teaching activities

We teach the 3rd year medical students (M1) about genomics, genomic medicine, and genetic counseling as part of “General Pathology” and “Medical Engineering Lectures”. For M4 medical students who come to the Department of Clinical Genomics for a one-month rotation in fiscal year, we give lectures and opportunities to participate in genetic counseling and molecular tumor board (Expert Panels) under collaboration with “Next-Generation Precision Medicine Development Laboratory”, “Department of Pathology”, “Department of Clinical Laboratory”, and many other related clinical departments. As for PhD students, our laboratory take part in the lecture of “Clinical Oncology”.

Basic Research

- (1) Genome-wide analysis of cancer
 - a. Whole-genome sequencing, whole-exome sequencing, Comprehensive Genomic Profiling

- b. Multi-omics (Copy Number Variation Analysis, RNA-sequencing, Methylation Array, etc)
- c. Liquid biopsy (with circulating tumor cells, cell-free tumor DNA, DNA from ascites, etc)
- d. Analysis of hereditary cancer syndromes (Genetic testing and NGS-based comprehensive analysis)

(2) Development of a novel NGS-based cancer genomic profiling panel (Todai OncoPanel2)

- a. Analysis of quality of DNA and RNA from FFPE (formalin-fixed paraffin-embedded) specimens.
- b. Prospective analysis of various cancers for clinical application.
- c. Evaluation of microsatellite instability and genomic instability

(3) Exploration of biomarkers for molecular-targeted drugs

- a. Evaluation of homologous recombination deficiency by using mutational signatures
- b. Biomarkers for immune checkpoint inhibitors
- c. Classification by expression signature
- d. Drug sensitivity screening by using patient-derived models

Translational Research

(1) Todai OncoPanel and Genomic Medicine in Cancer

Trial of a multiplex genomic testing by "Todai OncoPanel" for Geneprofiling of malignant solid tumors as Advanced Medical Care Category B was performed in 200 cancer patients (from 2018 to 2020).

UMIN000033647

Todai OncoPanel (TOP) has been originally established at the University of Tokyo (by Professor Hiroyuki Mano (currently Director of National Cancer Center Research Institute) and Professor Hiroyuki Aburatani et al), which is composed of DNA panel (version 3: 464 genes) and RNA panel (version 4: 463 genes). We reported the usefulness of TOP panel, especially in detecting gene fusions, including *ALK*, *ROS1*, and *NTRK*.

(2) Investigator-Initiated Clinical Trial using a PARP inhibitor, entitled “A multi-center, phase II study of Olaparib maintenance therapy in patients with high-grade ovarian cancer, combined with translational research by integrated genome-wide analysis”

This study assesses the efficacy of olaparib maintenance monotherapy in high-grade and stage IIIC/IV ovarian cancer patients (including patients with primary peritoneal and / or fallopian tube cancer) with “BRCA-related biomarker” that is predicted by whole-exome sequencing of fresh-frozen tumor samples.

(3) Enrollment to the prospective trial of patient-proposed healthcare services with multiple targeted agent based on the result of gene profiling by multigene panel test. (BELIEVE) : jRCTs031190104

Clinical activities are described in the section of “Department of Clinical Genomics”.

Publications

1. Ohara K, Miyawaki S, Nakatomi H, Okano A, Teranishi Y, Shinya Y, Ishigami D, Hongo H, Takayanagi S, Tanaka S, Shinozaki-Ushiku A, Kohsaka S, Kage H, Oda K, Miyagawa K, Aburatani H, Mano H, Tatsuno K, Saito N: Case report and literature review: exploration of molecular therapeutic targets in recurrent malignant meningioma through comprehensive genetic analysis with Todai OncoPanel. *Front Neurol* **14**:1270046, 2023.
2. Suzuki M, Kasajima R, Yokose T, Shimizu E, Hatakeyama S, Yamaguchi K, Yokoyama K, Katayama K, Yamaguchi R, Furukawa Y, Miyano S, Imoto S, Shinozaki-Ushiku A, Ushiku T, Miyagi Y: KMT2C expression and DNA homologous recombination repair factors in lung cancers with a high-grade fetal adenocarcinoma component. *Transl Lung Cancer Res* **12**:1738-1751, 2023.
3. Kobayashi H, Zhang L, Okajima K, Ishibashi Y, Hirai T, Tsuda Y, Ikegami M, Kage H, Shinozaki-Ushiku A, Oda K, Tanaka S: BRAF mutations and concurrent alterations in patients with soft tissue sarcoma. *Genes Chromosomes Cancer* **62**:648-654, 2023.
4. Rai Y, Umekawa M, Shinya Y, Hasegawa H, Katano A, Kondo K, Shinozaki-Ushiku A, Saito N: Stereotactic radiosurgery for recurrent skull base polymorphous adenocarcinoma invading the cavernous sinus: illustrative case. *J Neurosurg Case Lessons* **5**: CASE23103:, 2023.
5. Nakagawa N, Kawakami M, Suzuki M, Noguchi S, Mitani A, Tanaka G, Shinozaki-Ushiku A, Nagase T: Pulmonary carcinoid tumour with remarkably high levels of pro-gastrin-releasing peptide: A case report. *Respir Med Case Rep* **43**:101836, 2023.
6. Yoshida D, Kamiya M, Kawashima S, Yoshioka T, Hino H, Abe A, Fujita K, Kojima R, Shinozaki-Ushiku A, Urano Y, Nakajima J: Rapid imaging of thymoma and thymic carcinoma with a fluorogenic probe targeting glutamyltranspeptidase. *Sci Rep* **13**:3757, 2023.
7. Abe K, Anzai H, Eguchi S, Ikemura M, Shinozaki-Ushiku A, Shinagawa T, Sonoda H, Yoshioka Y, Nagai Y, Abe S, Matsuzaki H, Yokoyama Y, Emoto S, Muroto K, Sasaki K, Nozawa H, Ushiku T, Ishihara S: Metastasis of Ovarian Cancer to the Descending Colon. *Case Rep Gastroenterol* **17**:129-136, 2023.
8. Kondo A, Shinozaki-Ushiku A, Rokutan H, Kunita A, Ikemura M, Yamashita H, Seto Y, Nagae G, Tatsuno K, Aburatani H, Koinuma D, Ushiku T: Loss of viral genome with altered immune microenvironment during tumour progression of Epstein-Barr virus-associated gastric carcinoma. *J Pathol* **260**:124-136, 2023.
9. Kikuchi R, Emoto S, Nozawa H, Sasaki K, Muroto K, Abe S, Sonoda H, Shinozaki-Ushiku A, Ishihara S: Jejunal intussusception and

- perforation due to enteric muco-submucosal elongated polyp: a case report and literature review. *Surg Case Rep* **9**:4, 2023.
10. Xi Q, Kage H, Ogawa M, Matsunaga A, Nishijima A, Sone K, Kawana K, Oda K: Genomic Landscape of Endometrial, Ovarian, and Cervical Cancers in Japan from the Database in the Center for Cancer Genomics and Advanced Therapeutics. *Cancers (Basel)* **16** (1):136, 2023.
 11. Tsuchimochi S, Wada-Hiraike O, Urano Y, Kukita A, Yamaguchi K, Honjo H, Taguchi A, Tanikawa M, Sone K, Mori-Uchino M, Tsuruga T, Oda K, Osuga Y: Characterization of a fluorescence imaging probe that exploits metabolic dependency of ovarian clear cell carcinoma. *Sci Rep* **13**:20292, 2023.
 12. Shigeta S, Shimada M, Suzuki S, Kajiyama H, Oda K, Takehara K, Mandai M, Aoki D, Enomoto T, Okamoto A: An Attempt to Develop a New Treatment Strategy for Rare Refractory Gynecological Malignancies: The Japanese Gynecologic Oncology Group. *JMA J* **6**:527-531, 2023.
 13. Saito Y, Kage H, Kobayashi K, Yoshida M, Fukuoka O, Yamamura K, Mukai T, Oda K, Yamasoba T: TERT promoter mutation positive oral cavity carcinomas, a clinically and genetically distinct subgroup of head and neck squamous cell carcinomas. *Head Neck* **45**(12): 3107-3118, 2023.
 14. Kobayashi K, Saito Y, Kamogashira T, Kage H, Fukuoka O, Yamamura K, Mukai T, Oda K, Yamasoba T: Survival analysis of high-grade salivary gland carcinoma adjusted for length bias due to delay in comprehensive genomic profiling. *Jpn J Clin Oncol* **53**:1092-1093, 2023.
 15. Matsubara J, Mukai K, Kondo T, Yoshioka M, Kage H, Oda K, Kudo R, Ikeda S, Ebi H, Muro K, Hayashi R, Tokudome N, Yamamoto N, Muto M: First-Line Genomic Profiling in Previously Untreated Advanced Solid Tumors for Identification of Targeted Therapy Opportunities. *JAMA Netw Open* **6**:e2323336, 2023.
 16. Kobayashi K, Saito Y, Kage H, Fukuoka O, Yamamura K, Mukai T, Oda K, Yamasoba T: CDK12 alterations and ARID1A mutations are predictors of poor prognosis and therapeutic targets in high-grade salivary gland carcinoma: analysis of the National Genomic Profiling Database. *Jpn J Clin Oncol* **53**:798-807, 2023.
 17. Kage H, Oda K, Muto M, Tsuchihara K, Okita N, Okuma Y, Kikuchi J, Shiota H, Hayashi H, Kokuryo T, Sakai D, Hirasawa A, Kubo M, Kenmotsu H, Akiyama N, Shinozaki-Ushiku A, Tanabe M, Ushiku T, Miyagawa K, Seto Y: Human resources for administrative work to carry out a comprehensive genomic profiling test in Japan. *Cancer Sci* **114**:3041-3049, 2023.
 18. Yoshihara K, Baba T, Tokunaga H, Nishino K, Sekine M, Takamatsu S, Matsumura N, Yoshida H, Kajiyama H, Shimada M, Kagimura T, Oda K, Sasajima Y, Yaegashi N, Okamoto A, Sugiyama T, Enomoto T: Homologous recombination inquiry through ovarian malignancy investigations: JGOG3025 Study. *Cancer Sci* **114**:2515-2523, 2023.
 19. Kusakabe M, Taguchi A, Tanikawa M, Hoshi D, Tsuchimochi S, Qian X, Toyohara Y, Kawata A, Wagatsuma R, Yamaguchi K, Yamamoto Y, Ikemura M, Sone K, Mori-Uchino M, Matsunaga H, Tsuruga T, Nagamatsu T, Kukimoto I, Wada-Hiraike O, Kawazu M, Ushiku T, Takeyama H, Oda K, Kawana K, Hippo Y, Osuga Y: Application of organoid culture from HPV18-positive small cell carcinoma of the uterine cervix for precision medicine. *Cancer Med* **12**:8476-8489, 2023.
 20. Komura A, Taguchi A, Ikemura M, Nishijima A, Miyamoto Y, Tanikawa M, Sone K, Mori M, Oda K, Osuga Y: A case of refractory pelvic squamous cell carcinoma of unknown primary that responded to nivolumab. *J Obstet Gynaecol Res* **49**:1300-1304, 2023.
 21. Kage H, Shinozaki-Ushiku A, Ishigaki K, Sato Y, Tanabe M, Tanaka S, Tanikawa M, Watanabe K, Kato S, Akagi K, Uchino K, Mitani K, Takahashi S, Miura Y, Ikeda S, Kojima Y, Watanabe K, Mochizuki H, Yamaguchi H, Kawazoe Y, Kashiwabara K, Kohsaka S, Tatsuno K, Ushiku T, Ohe K, Yatomi Y, Seto Y, Aburatani H, Mano H, ORCID: 0000-0003-4645-0181, Miyagawa K, Oda K: Clinical utility of Todai OncoPanel in the setting of approved comprehensive cancer genomic profiling tests in Japan. *Cancer Sci*

114:1710-1717, 2023.

22. Takamatsu S, Yoshihara K, Baba T, Shimada M, Yoshida H, Kajiyama H, Oda K, Mandai M, Okamoto A, Enomoto T, Matsumura N: Prognostic relevance of HRDness gene expression signature in ovarian high-grade serous carcinoma; JGOG3025-TR2 study. *Br J Cancer* **128**:1095-1104, 2023.
23. Mizuno S, Ikegami M, Koyama T, Sunami K, Ogata D, Kage H, Yanagaki M, Ikeuchi H, Ueno T, Tanikawa M, Oda K, Osuga Y, Mano H, Kohsaka S: High-Throughput Functional Evaluation of MAP2K1 Variants in Cancer. *Mol Cancer Ther* **22**:227-239, 2023.
24. Kusakabe M, Taguchi A, Tanikawa M, Wagatsuma R, Yamazaki M, Tsuchimochi S, Toyohara Y, Kawata A, Baba S, Ueno T, Sone K, Mori-Uchino M, Ikemura M, Matsunaga H, Nagamatsu T, Wada-Hiraike O, Kawazu M, Ushiku T, Takeyama H, Oda K, Kawana K, Mano H, Osuga Y: Cells with stem-like properties are associated with the development of HPV18-positive cervical cancer. *Cancer Sci* **114**:885-895, 2023.

Neuroscience

1. Basic Neuroscience

Department of Neuropathology

Professor

Takeshi Iwatsubo, M.D., Ph.D.

Lecturer

Tomoki Kuwahara, Ph.D.

Associate

Kaoru Yamada, Ph.D.

Kenichiro Sato, M.D., Ph.D.

※The following information is the same as that of the previous year for certain reasons.

Homepage <http://www.neuropathology.m.u-tokyo.ac.jp/>

Dr. Iwatsubo's research group has been pursuing the pathogenesis of Alzheimer's disease (AD) and related neurodegenerative conditions (especially, dementia with Lewy bodies; DLB) by multi-disciplinary approaches, based on histopathology and protein biochemistry of postmortem human brains. They then extended the knowledge derived from the human studies in a way to establish cellular models and to elucidate the key steps in the pathological cascade of neurodegeneration. Thus, Dr. Iwatsubo's group has been addressing the pathogenesis of neurodegenerative disorders from the downstream (i.e., analysis of aggregated proteins) as well as from the upstream (i.e., pathogenic effects of pathogenic genes), covering a number of crucial proteins/genes related to AD and DLB, i.e., β -amyloid (including its binding protein CLAC), presenilin/ γ -secretase and α -synuclein. In this way Dr. Iwatsubo's group has contributed much to the widely accepted notion that abnormal misfolding of brain proteins is the common cause of a variety of neurodegenerative disorders including AD. Furthermore, Dr. Iwatsubo's group is currently working hard to translate the basic findings into the clinical application of mechanism-based, disease-modifying therapies for AD through the world-wide ADNI project, in which Dr. Iwatsubo serves as the PI of Japanese ADNI.

1. Research on β -amyloid and presenilins

Using C-terminal specific monoclonal antibodies that discriminate amyloid β peptides ($A\beta$) ending at 40th or 42nd residues ($A\beta_{40}$ and $A\beta_{42}$, respectively), Dr. Iwatsubo has performed a systematic immuno-histochemical studies on autopsied brain tissues from patients with AD, Down syndrome and familial AD, and demonstrated that $A\beta_{42}$, that most readily form amyloid fibrils in vitro, is the initially and predominantly deposited species in human cerebral β -amyloidosis (Iwatsubo et al. Neuron 1994, Ann Neurol 1995). Dr. Iwatsubo's group then established cellular models expressing mutant forms of presenilin (PS) genes linked to familial AD (FAD), and using their original highly-sensitive ELISA quantitation system, his group has clearly shown that an increase in the production of $A\beta_{42}$ is the pathogenic mechanism leading to FAD (Tomita et al. Proc Natl Acad Sci USA, 1997). These findings have provided a firm basis for the currently prevailing β -amyloid hypothesis. They then focused on the mechanisms of γ -secretase complex that cleaves the C terminus of $A\beta$, and set out to cell biological studies using RNA interference on the formation and function of the γ -secretase complex harboring PS as the catalytic center, associated with three additional membrane

proteins. They demonstrated that A β -1 and Nicastrin serve as the “stabilizing” co-factor of PS, whereas PEN-2 is the component that confers proteolytic activity to this complex. They also showed that PS, A β -1, nicastrin and PEN-2 are the essential set of proteins that comprise the γ -secretase complex (Takasugi et al. *Nature*, 2003). This study is highlighted as a milestone work that elucidated the mechanistic roles of protein cofactors in the formation and function of γ -secretase (see reviews; Iwatsubo *Mol Psychiatr*, 2004; *Curr Opin Neurobiol*, 2004). His group has established an elegant strategy to analyze the structure-function relationship within the catalytic structure of γ -secretase complex by cysteine chemistry, and demonstrated that γ -secretase harbors a water-permeable catalytic pore (Sato et al. *J Neurosci*, 2006), and that substrate proteins enter the catalytic pore through the lateral gate located at the C terminal side of PS (Sato et al. *J Neurosci*, 2008). Thus, Dr. Iwatsubo’s group started from an elegant immunohistochemical analysis of A β deposits in AD brains and extended it to a contemporary molecular/cellular biology of PS, that proved to play a key role in “intramembrane proteolysis”.

2. Identification and characterization of α -synuclein as a major component of Lewy bodies.

Using cortical Lewy bodies purified from postmortem brains of patients with dementia with Lewy bodies (DLB) by his original method (Iwatsubo et al. *Am J Pathol* 1996) as immunogens, Dr. Iwatsubo’s group, in collaboration with Drs. Virginia Lee and John Trojanowski at Univ. Penn, performed an extensive immunochemical search for components of Lewy bodies. They have demonstrated by raising a specific monoclonal antibody that α -synuclein, that proved to be a product of pathogenic gene for familial form of Parkinson’s disease, is one of the major constituent of Lewy bodies in sporadic Parkinson’s disease and DLB (Baba et al. *Am J Pathol* 1998). His group then purified aggregated α -synuclein from DLB cortices using fine biochemical techniques, purified it to near homogeneity, and demonstrated using mass spectrometry and specific antibodies that α -synuclein deposited in synucleinopathy lesions is highly phosphorylated at a specific serine residue (Fujiwara et al. *Nature Cell Biol* 2002). This finding led to a

range of studies focusing on the role of synuclein phosphorylation in neurodegeneration. Also, the phospho-specific α -synuclein antibody is widely used as the most sensitive marker for α -synucleinopathy lesions, and has characterized a wide spectrum of α -synuclein pathologies in neurodegenerative disorders.

3. Identification of a non-A β Alzheimer amyloid plaque component CLAC, and its precursor CLAC-P

The major component of Alzheimer’s amyloid plaques is A β , although there are a number of non-A β components that potentially affect fibrillization and degradation of amyloid deposits. Among these, there has been an enigmatic “missing piece” protein of molecular masses of 50/100 kDa. Dr. Iwatsubo’s group raised a monoclonal antibody against amyloid fraction that recognizes this protein, and using this antibody as a probe, they conducted a thorough biochemical purification of these antigens and finally cloned a cDNA coding for the precursor of this protein. This protein turned out to be a novel class of membrane-bound collagen, which was named CLAC (collagen-like Alzheimer amyloid plaque component) and its precursor CLAC-P (Hashimoto et al. *EMBO J* 2002). This finding had an immense impact both on fields of AD research as well as on general biology as a first discovery of neuron-specific collagen harboring a unique membrane-spanning structure. CLAC has been highlighted as a protein that may affect fibrillization of A β and contribute to amyloid plaque formation. Indeed, he has recently shown that CLAC-positive senile plaques constitute a unique subset of plaques distinct from the classical, β -sheet-rich amyloid deposits, underscoring the pathobiological role of CLAC in amyloid formation, and that CLAC inhibits fibrillization of A β in vitro. Knockout mice studies have confirmed the role of CLAC in neuromuscular development (Munezane et al. *Cell Reports*, 2019).

4. Glymphatic system and tau clearance

Accumulation of tau has been implicated in various neurodegenerative diseases termed tauopathies. Tau is a microtubule-associated protein but is also actively released into the extracellular fluids including brain interstitial fluid and cerebrospinal fluid (CSF). However, it remained

elusive whether clearance of extracellular tau impacts tau-associated neurodegeneration. We showed that aquaporin-4 (AQP4), a major driver of the glymphatic clearance system, facilitates the elimination of extracellular tau from brain to CSF and subsequently to deep cervical lymph nodes. Strikingly, deletion of AQP4 not only elevated tau in CSF but also markedly exacerbated phosphorylated tau deposition and associated neurodegeneration in the brains of transgenic mice expressing P301S mutant tau. We thus identified the clearance pathway of extracellular tau in the central nervous system, suggesting that glymphatic clearance of extracellular tau is a novel regulatory mechanism whose impairment contributes to tau aggregation and neurodegeneration.

5. Japanese ADNI and development of disease-modifying therapies against AD

Basic studies on the pathomechanism of AD have boosted the development of mechanism-based drugs for AD, whereas the bottleneck has been the lack of surrogate biomarkers that represent the progression of AD pathology and are useful in the clinical trial of disease-modifying drugs. In close collaboration with Drs. Mike Weiner and Ron Petersen of US-ADNI, Dr. Iwatsubo has initiated the Japanese ADNI as the principal investigator on 2006, recruiting 38 clinical sites nationwide, and preparing all the infrastructures required for the large-scale clinical study. The J-ADNI group recruit 537 individuals in total, and all the data derived from the J-ADNI study have been made in public from the National Bioscience Database Center for research use. Recently, the J-ADNI group has demonstrated the similarity between MCI due to AD in Asian and Caucasian populations by comparing the clinical and biomarker features of J-ADNI and ADNI participants, supporting the feasibility of global clinical trials of disease-modifying therapies for AD. Recently, his group is leading the “Japanese Trial-Ready cohort for prevention of AD (J-TRC). These efforts have led to the successful development of anti-amyloid antibody therapies against AD in 2023.

References

- 1) An H, Litscher G, Watanabe N, Wei W, Hashimoto T, Iwatsubo T, Buchman VL, Shelkovnikova T: ALS-linked cytoplasmic FUS assemblies are compositionally different from physiological stress granules and sequester hnRNPA3, a novel modifier of FUS toxicity. *Neurobiol Dis* 162:105585, 2022
- 2) Kazawa K, Akishita M, Ikeda M, Iwatsubo T, Ishii S: Experts’ perception of support for people with dementia and their families during the COVID-19 pandemic. *Geriatr Gerontol Int* 22: 26-31, 2022
- 3) Rotstein A, Levine SZ, Samara M, Yoshida K, Goldberg Y, Cipriani A, Iwatsubo T, Leucht S, Furawaka TA: Cognitive impairment networks in Alzheimer’s disease: Analysis of three double-blind randomized, placebo-controlled, clinical trials of donepezil. *Eur Neuropsychopharmacol* 57:50-58, 2022
- 4) Levine SZ, Goldberg Y, Yoshida K, Efthimiou O, Samara M, Cipriani A, Iwatsubo T, Leucht S, Furawaka TA: Early- and subsequent- response of cognitive functioning in Alzheimer’s disease: Individual-participant data from five pivotal randomized clinical trials of donepezil. *J Psychiatr Res* 148:159-164, 2022
- 5) Ishida K, Yamada K, Nishiyama R, Hashimoto T, Nishida I, Abe Y, Yasui M, Iwatsubo T: Glymphatic system clears extracellular tau and protect from tau aggregation and neurodegeneration. *J Exp Med* 219:e20211275, 2022
- 6) Kaneshiro N, Komai M, Imaoka R, Ikeda A, Kamikubo Y, Hashimoto T, Iwatsubo T, Sakurai T, Uehara T, Takasugi N: Lipid flippase dysfunction as a novel therapeutic target for endosomal anomalies in Alzheimer’s disease. *iScience* 25: 103869, 2022
- 7) Haeberlein SB, Aisen PS, Barkhof F, Chalkias S, Chen T, Cohen S, Dent G, Hansson O, Harrison K, von Hehn C, Iwatsubo T, Mallinckrodt C, Mummery CJ, Muralidharan KK, Nestorov I, Nisenbaum L, Rajagovindan R, Skordos L, Tian Y, van Dyck CH, Vellas B, Wu S, Zhu Y, Sandrock A: Two randomized phase 3 studies to evaluate aducanumab in early Alzheimer disease. *J Prev Alzheimers Dis* 9:197-210, 2022
- 8) Tsujikawa K, Hamanaka K, Riku Y, Hattori Y, Hara N, Iguchi Y, Ishigaki S, Hashizume A,

- Miyatake S, Mitsuhashi S, Miyazaki Y, Kataoka M, Jiayi L, Yasui K, Kuru S, Koike H, Kobayashi K, Sahara N, Ozaki N, Yoshida M, Kakita A, Saito Y, Iwasaki Y, Miyashita A, Iwatsubo T, Ikeuchi T, Miyata T, Sobue G, Matsumoto N, Sahashi K, Katsuno M: Actin-1 binding protein filamin-A drives tau aggregation and contributes to progressive supranuclear palsy pathology. *Sci Adv* 8:eabm5029, 2022
- 9) Sato K, Niimi Y, Mano T, Iwata A, Iwatsubo T: Time to onset of drug-induced parkinsonism: Analysis using a large Japanese adverse event self-reporting database. *Biosci Trends* 16:151-157, 2022
 - 10) Sato K, Niimi Y, Mano T, Iwata A, Iwatsubo T: Automated evaluation of conventional clock-drawing test using deep neural network: potential as a mass screening tool to detect individuals with cognitive decline. *Front Neurol* 13:896403, 2022
 - 11) Kishino Y, Matsukawa K, Matsumoto T, Wakabayashi T, Nonaka T, Kametani F, Hasegawa M, Hashimoto T, Iwatsubo T: Casein kinase 1 δ/ϵ phosphorylates fused in sarcoma (FUS) and ameliorates FUS-mediated neuro-degeneration. *J Biol Chem* 298: 102191, 2022
 - 12) Poulakis K, Pereira JB, Muehlboeck J-S, Wahlund L-O, Smedby Ö, Volpe G, Masters CL, Ames D, Niimi Y, Iwatsubo T, Ferreira D, Westman E: Stage vs. Subtype hypothesis in Alzheimer's disease: a multi-cohort and longitudinal Bayesian clustering study. *Nat Commun* 13:4566, 2022
 - 13) Kasuga K, Kikuchi M, Tsukie T, Suzuki K, Ihara R, Iwata A, Hara N, Miyashita A, Kuwano R, Iwatsubo T, Ikeuchi T: Characterization of ATN profile classified using two different N markers in CSF. *BMJ Neurol Open* 4:e000321, 2022
 - 14) Sato K, Niimi Y, Iwatsubo T, Ishii S: Change in long-term care service usage in Japan following the COVID-19 pandemic: a survey using a nationwide statistical summary in 2018–2021. *Geriatr Gerontol Int* 22:803-809, 2022
 - 15) de Erausquin GA, Snyder HM, Brugha TS, Seshadri S, Carrillo M, Sagar R, Huang Y, Newton C, Tartaglia C, Teunissen C, Håkanson K, Akinyemi R, Prasad K, D'Avossa G, Gonzalez-Aleman G, Hosseini A, Vavougiou GD, Sachdev P, Bankart J, Ole Mors NP, Lipton R, Katz M, Fox PT, Katshu MZ, Iyengar MS, Weinstein G, Sohrabi HR, Jenkins R, Stein DJ, Hugon J, Mavreas V, Blangero J, Cruchaga C, Krishna M, Wadood O, Becerra R, Zwir I, Longstreth WT, Kroenke G, Edison P, Mukaetova-Ladinska E, Staufenberg E, Figueredo-Aguiar M, Yécora A, Vaca F, Zamponi HP, Lo Re V, Majid A, Sundarakumar J, Gonzalez HM, Geerlings MI, Skoog I, Salmoiraghi A, Boneschi FM, Patel VN, Santos JM, Arroyo GR, Moreno AC, Felix P, Gallo C, Arai H, Yamada M, Iwatsubo T, Sharma M, Chakraborty N, Ferreccio C, Akena D, Brayne C, Maestre G, Blangero SW, Brusco LI, Siddarth P, Hughes TM, Zuñiga AR, Kambeitz J, Laza AR, Allen N, Panos S, Merrill D, Ibáñez A, Tsuang D, Valishvili N, Shrestha S, Wang S, Padma V, Anstey KJ, Ravindranath V, Blennow K, Mullins P, Łojek E, Pria A, Mosley TH, Gowland PG, Girard TD, Bowtell R, Vahidy FS: Chronic neuropsychiatric sequelae of SARS-CoV2: Protocol 1 and methods from the Alzheimer's Association Global Consortium. submitted to *Alzheimers Dementia: Translational Research & Clinical Interventions* 8:e12348, 2022
 - 16) Yoshida K, Seo M, Yan L, Sahker E, Cipriani A, Leucht S, Iwatsubo T, Efthimiou O, Furukawa TA: Personalized prediction of Alzheimer's disease and its treatment effects by donepezil: an individual participant data meta-analysis of eight randomized controlled trials. *J Alz Dis* 89:1143-1157, 2022

Department of Neurochemistry

Professor and Head

Haruhiko Bito, M.D., Ph.D.

Lecturer

Hajime Fujii, Ph.D.

Assistant Professor

Ryang Kim, Ph.D., Keisuke Ota, Ph.D.

Homepage <http://www.neurochem.m.u-tokyo.ac.jp/Homepage.html>

Introduction and Organization

Our Department's primary goal is to elucidate the basic signal transduction mechanisms which mediate key processes underlying various brain functions, such as learning, memory or emotion. A fundamental question is how an ensemble behavior of 10~100 billion neurons can possibly give rise to a coherent and integrated "brain" that controls the whole human organism for a period of more than eighty years. Our central nervous system is physically wired and organized based on evolutionary and developmental principles that are primarily encoded into the genome and that are highly conserved in mammals from rodents to primates. This neural network, however, is able to recognize and memorize external and internal events as they occur. And furthermore, brain function, especially human's, stands out by its intrinsic capacity to extract patterns and rules from these events, and to consciously associate them with abstract meaning and affective valence, while also unconsciously facilitating coordinated body responses.

Neurochemistry once used to be a relatively dull discipline consisting of analyzing substances that form the brain. However, it has recently become a field of excitement where we are now (almost) able to measure changes in cellular messengers or modifications in signaling molecules in critical parts of the neurons such as the dendritic spines or the axon terminals, as the neurons summate synaptic potentials or fire action potentials.

What are the precise nature and the whole spectrum of the molecular changes in the neurons that undergo heavy or patterned electrical activity? What are the molecular rules that govern these local and global changes, both electrical and chemical? How are these events, in turn, converted into more profound modifications of the synaptic wiring mechanisms? And finally do these alterations genuinely underlie certain kinds of information processing and storage?

To address these issues, this Department currently focuses its resources into two basic aims:

- 1) Molecular investigation (including identification, characterization and real-time visualization) of signaling molecules involved in calcium-dependent synaptic modification, especially during signaling from synapse-to-nucleus, and back from nucleus-to-synapses.
- 2) Understanding molecular mechanisms controlling cytoskeletal dynamics and remodeling on both sides of the synapses, in the dendritic spines and in axon terminals.

Following the retirement of Professor Tatsuya Haga (who became the President of Life Sciences Institute at the Faculty of Science at Gakushuin University) in March 2001, and the departure of Associate Professor David Saffen to initially University of Minnesota and then to Ohio State University in August 2001, Associate Professor Haruhiko Bito was appointed as Head of Department since January 2003. The Department is located on the 6th floor, in the West

wing of the third building of the Medical School. The Department currently enrolls one professor, one lecturer, two assistant professors, one postdoctoral scholar, one technical staff, ten Ph.D. graduate students, one research student, one technical assistant, one research technician and two administrative assistants.

Teaching activities

The Department's teaching activities include:

- 1) Introductory Neuroscience coursework provided to pre-medical students in the Komaba campus (one hour);
- 2) Neurochemistry lectures to medical students as part of the "Biochemistry- Molecular Biology- Nutrition" core curriculum (two hours);
- 3) Introductory Molecular and Cellular Neuroscience, and Basic Neurochemistry lectures to first-year master degree students (three hours);
- 4) Organization of the lecture course: "Basic Neuroscience" (Molecular and Cellular Neuroscience) (a lecture series with fifteen lectures from outstanding neuroscientists from all over Japan).

Additionally, Neurochemistry Seminars are frequently and regularly organized that enables direct exposure of Ph.D. graduate students and postdocs to both young promising researchers and established investigators from all over the world.

Research activities

The Department of Neurochemistry currently focuses its resources into two core projects:

- 1) Molecular investigation (including identification, characterization and real-time visualization) of signaling molecules involved in calcium-dependent synaptic modification, especially during signaling from synapse-to-nucleus, and back from nucleus-to-synapses.

Changes in efficacy of synaptic transmission have been shown to strongly correlate with functional plasticity of many brain circuits including the hippocampus, the amygdala, the striatum, the neocortex, the cerebellum or the spinal cord. An early phase of long-term synaptic plasticity is induced by virtue of specific post- and/or presynaptic modifi-

cations of the biochemical machinery dedicated to synaptic release and neurotransmitter recognition. It then is expressed by bistable mechanisms that are strongly governed and dictated by the pattern of synaptic calcium influxes experienced during the initial conditioning period. While the molecular identity of the involved synaptic proteins is now (almost) being solved (or is becoming much less controversial than before), several essential questions remain unanswered.

The "Old" question was: What are the molecular determinants that enable these plastic changes to be induced and maintained locally? Yet, related issues of critical importance that still remain wide open questions are:

- 1) What are the full-range of calcium-triggered molecular signaling cascades which are activated at and near the potentiated/depressed synapses? And how do they influence plasticity per se?
- 2) What is the contribution of activity-dependent gene expression in prolongation and consolidation of such synapse-restricted changes?

In order to begin to address these issues, we have been investigating in particular the role of several calcium-calmodulin dependent protein kinases.

We previously showed the critical importance of a CaMKK/CaMKIV cascade in triggering synaptically-stimulated nuclear CREB phosphorylation in hippocampal neurons. The extreme biochemical efficacy and the relative poor frequency-dependence of this signaling cascade, in combination with the robust correlation between prolonged pCREB response and downstream gene expression led us to propose that CaMKK/CaMKIV/pCREB cascade was likely to act as a critical temporal integrator for activity-dependent gene expression in excitatory neurons (Bito et al., Cell, 1996; Bito et al., Curr. Opin. Neurobiol., 1997; Bito, Cell Calcium, 1998). This hypothesis has now been critically tested in various brain systems and indeed pCREB immunofluorescence is now considered as a universal marker for integrated synaptic activity that is more sensitive than that of c-Fos (Nonaka, J. Neurosci. 2009). The critical function of CaMKK/CaMKIV/pCREB cascade in the expression of long-term synaptic plasticity was also validated in long-term potentiation in the hippocampus (Redondo et al., J Neurosci. 2010).

Furthermore, CaMKIV-KO, CaMKK-KO and CaMKIV-dominant negative transgenic studies by many laboratories have confirmed the critical role for CaMKIV as synaptic activity-triggered CREB kinase.

We subsequently also showed that CaMKIV in the cerebellar granule cells played a critical role in tuning the pCREB response necessary for depolarization-mediated neuronal survival, and that in fact CaMKIV stability was actively maintained by depolarization. Loss of depolarizing signal led to a caspase-mediated proteolytic degradation of CaMKIV. This in turn severely impaired CREB phosphorylation, facilitating apoptosis, and conversely rescuing pCREB by overexpressing an active form of CaMKIV was sufficient to prevent apoptosis (See et al., *FASEB J.*, 2001). Consistent with our observation that subtle CREB regulation may underlie the neuronal cell survival, CREB-dependent gene expression mechanisms, especially CBP regulation, have actually been proposed to be affected in one way or another in many neurodegenerative disorders such as hereditary polyglutamine diseases. We thus speculated that if CREB-opathies (or various defects in CREB-mediated gene activation mechanisms) were critical determinants in exacerbating neurodegeneration, certain disease forms may actually accompany deficit in CaMKIV/pCREB signaling (Bito and Takemoto-Kimura, *Cell Calcium* 2003). We also identified kinase/phosphatase signaling responsible for activity-dependent nuclear trafficking of CRTC1, a key cofactor of CREB, and demonstrated its roles in CREB-dependent transcription and contextual fear memory in amygdala (Nonaka et al., *Neuron* 2014).

To elucidate the significance of the genes regulated downstream of CREB during learning and memory, we set out to uncover the most elementary regulatory element required and sufficient to trigger robust activity-dependent gene induction of the immediate early gene *Arc*, whose expression in many brain areas have been invariably associated with key cognitive activities mediated by these areas. We discovered a fundamentally novel synaptic activity-responsive element (SARE) which was present as a distal regulatory promoter element and was conserved across most mammalian species (Kawashima et al., *PNAS* 2009; Kim et al., *Nature* 2010; Inoue et al., *Commun. Integr. Biol.* 2010). Surprisingly, SARE

contained juxtaposed binding elements for all three activity-regulated transcription factors, CREB, MEF2 and SRF. The identification of SARE enables us to build reporter virus and mouse lines that are expected to be useful to map the extent of neuronal circuit activation during various kinds of cognitive activities (Kawashima et al., *Nat. Methods* 2013). In addition to the transcriptional regulation, we are currently investigating about the physiological function and its molecular mechanism of *Arc*, which is thought to be a key player that contributes activity dependent neuronal plasticity at post synaptic sites (Okuno et al., *Cell* 2012).

One parallel branch of CaMK signaling that has not been widely studied is the CaMKK/CaMKI pathway. During the search for potential CaMKIV-like CREB regulatory kinases (CLICKs) (Ohmae et al., *J. Biol. Chem.* 2006), we identified a novel CaMKI isoform that contained a C-terminal CAAX lipid modification motif (Takemoto-Kimura et al., *J. Biol. Chem.*, 2003; Takemoto-Kimura et al., *Neuron* 2007). This novel membrane-bound CaMK (CLICK-III/CaMKI γ) is most expressed in the central nucleus of the amygdala and in the ventral medial hypothalamus, while also being present at a much weaker amount in most central neurons. Biochemical and cell biological studies indicated a critical role for lipidification of this kinase to be properly sorted into specific lipid-restricted membrane microdomains. The function played by this lipidified, membrane-inserted CaMK in circuitry formation and maturation was scrutinized using RNA interference. Along with the identification of the critical lipid-modifying enzyme that controls lipid-anchoring of this kinase, we discovered a novel activity-regulated mechanism whereby CLICK-III/CaMKI γ is actively sorted into dendritic lipid rafts, where it specifically regulates Rac-mediated actin remodeling that is required for BDNF-stimulated dendritogenesis (Takemoto-Kimura et al., *Neuron*, 2007; Takemoto-Kimura et al. *Eur. J. Neurosci.* 2010). Similar studies in axonal growth also suggest the active contribution of CaMKK cascade in this process (Ageta-Ishihara et al., *J. Neurosci.* 2009; Takemoto-Kimura et al., *Eur. J. Neurosci.* 2010). Using a membrane-tethered genetically encoded calcium indicator, we successfully recorded spontaneous regenerative calcium transients (SRCaTs) in developing

mouse excitatory cortical neurons and discovered that L-type VGCCs play critical roles in neural development and corticogenesis (Kamijo et al., J. Neurosci. 2018).

How do these multiple Ca^{2+} -dependent signaling molecules process each pattern of intracellular Ca^{2+} dynamics to induce a cellular response? Recently, we have developed a method named dFOMA (dual FRET imaging with optical manipulation) to simultaneously measure activities of two distinct signaling molecules in living neurons. Applying originally developed FRET probes to dFOMA method enabled us to measure activities of CaMKII, calcineurin and Ca^{2+} , when a neuron received various frequencies of synaptic inputs. These experiments provided evidence that CaMKII α and calcineurin are fine-tuned to unique bandwidths and compute input variables in an asymmetric manner (Fujii et al., Cell Reports 2013; Fujii et al., Neurosci Res. 2022). We also applied the CaMKII FRET probe to elucidate the molecular mechanisms of intellectual disability caused by CAMK2A mutations and found a candidate therapeutic (Fujii et al., Front. Mol. Neurosci. 2022).

In line with the visualization of neuronal activity and Ca^{2+} signaling, we have developed R-CaMP2, a red genetically-encoded Ca^{2+} indicator that has single-action-potential sensitivity based on rational design that takes advantage of our long-standing effort and knowledge about CaMKK-CaMKIV signaling. By combining R-CaMP2 with green Ca^{2+} indicator G-CaMP, distinct activity patterns between excitatory and inhibitory neurons in somatosensory cortex was revealed (Inoue et al., Nat. Methods 2015). Furthermore, we have advanced our visualization probe technology to developed ultra-fast, ultra-sensitive Ca^{2+} indicators XCaMP-B/G/Y/R, which allowed imaging in blue, green, yellow, and red, and simultaneously tracked activities of high-frequency firing parvalbumin (PV)-positive cells, as well as activities of three different neuronal cell types (excitatory pyramidal cells, PV-positive and somatostatin (SST)-positive cells) (Inoue et al., Cell, 2019). We also developed knock-in mice expressing these novel Ca^{2+} indicators (Sakamoto et al., Cell Reports Methods 2022; Sakamoto et al., STAR Protocol, 2022).

One further important topic that we have been

focusing for a number of years is the role of gene expression in prolongation / consolidation of synapse-specific local changes. Neurons undergoing various stimulus patterns have been followed up in time and the amount of newly synthesized proteins and the local distribution of induced gene products have been monitored. Using state-of-the-art multi-wavelength fluorescence imaging techniques, we are now quantitatively assessing how local distribution of these newly synthesized gene products affect synaptic protein complexes (Okuno and Bito, AfCS/Nature Mol. Pages 2006).

2) Understanding molecular mechanisms controlling cytoskeletal dynamics and remodeling on both sides of the synapses, in the dendritic spines and in axon terminals.

Both synaptic maturation and synaptic plasticity have been shown to include a morphological component that is directed by the dynamics of actin cytoskeleton, a major cytoskeletal component both in the dendritic spines and at the very proximity of boutons in the axon terminals. Few studies in the past, however, had directly addressed what molecular determinants regulate actin dynamics in living central neurons undergoing synaptic activity. This was in part because actin filament assembly and disassembly were classically studied mostly at the moving edges of lamellipodia of large growth cones in large-size neurons from either mollusc or peripheral nerve cells. Such visualization turned out to be much more difficult in seemingly far less mobile spine structures tightly apposed to presynaptic active zones.

We (and others) used GFP-actin imaging to try to understand how neuronal actin cytoskeleton in hippocampal neurons was organized and reorganized by exposure to synaptic activity. In our dissociated culture system, virtually all spines contained a high amount of GFP-actin and most of them with few exceptions were apposed to FM4-64-positive active presynaptic termini. In these cultures, increases in synaptic glutamatergic transmission by repeated bursts of high-frequency synaptic activity clearly induced several distinct kinds of activity-dependent actin mobilization, including a slow but sustained synaptic delivery of GFP-actin in a non-negligible number of activated spines and a massive but transient

enhancement in cortical actin at the somatic periphery. The former was entirely dependent on NMDA-dependent Ca^{2+} -influx while the latter was likely to be mediated at least in part by L-type voltage-gated Ca^{2+} channel activity. Thus, distinct patterns and sources of Ca^{2+} influx were likely to trigger a complex spatially segregated patterns of actin cytoskeletal reorganization, with variable impact on either neuronal morphology and/or synaptic protein assembly (Furuyashiki et al., PNAS, 2002).

Similar studies are now ongoing in cerebellar Purkinje neurons, where spinogenesis is also subject to complex regulation during development, and where calcium dynamics is key to pre- and postsynaptic plasticity.

What are the key signaling pathways controlling actin dynamics in central neurons? We were especially keen to resolve the contribution of the small GTPase Rho and its downstream effectors, initially in the context of developmentally regulated neuronal morphogenesis. We first established in a model cell line N1E-115 that neurite retraction was directly linked to Rho/ROCK activity (Hirose et al., J. Cell Biol., 1998). We subsequently revealed that in central neurons, in addition to its essential role in regulating growth cone motility, Rho/ROCK activity in fact acted as a negative gate that tightly controls the timing with which the first processes are initiated out from the round cell soma (Bito et al., Neuron, 2000). Disruption of Rho/ROCK activity was sufficient to immediately initiate neuritogenesis. This indicated that endogenous Rho activators, by titrating ROCK activity, continuously antagonized process/ branch formation and that local gradient of Rho activators might play a crucial role in shaping the timing and the extent of process formation (Bito, J. Biochem., 2003). Consistent with this idea, we found that in cerebellar granule cells, a chemokine SDF-1 α released from the pia mater was likely to be a predominant Rho activator via stimulation of a cognate and specific GPCR CXCR4 (Arakawa et al., J. Cell Biol., 2003). While a true gradient in SDF-1 α still remains to be demonstrated in vivo, it is intriguing to note that most active axonal process formation and elongation actually occur in the inner zone of EGL that is opposite and most distant from the interface with the pia mater (Bito, J. Biochem., 2003). Most strikingly,

we demonstrated that axon elongation could actively occur in an intermediate Rho activity range that enables ROCK to be weakened enough while allowing another Rho effector mDial to actively mediate its effect on actin nucleation and polymerization (Arakawa et al., J. Cell Biol. 2003).

Whether similar or distinct mechanisms also operate during spinogenesis and spine maturation remains to be determined, though a role for Rho and ROCK has already been postulated in control of spine complexity and spine stability. However, multiple small GTPase signaling cascades clearly seem to contribute together, in a tightly coordinated manner, to spine regulation, since many distinct classes of GEFs and GAPs have now been shown to be localized in the dendritic spines. We ourselves initially reported the first two direct examples for PSD localization for such Rho small GTPases interacting proteins, Citron (Furuyashiki et al., J. Neurosci., 1999) and Cupidin/Homer2 (Shiraishi et al., J. Neurosci., 1999).

In an attempt to pin down molecular mechanisms that link PSD complexes and spine formation, we quantitatively examined the effect of deleting the binding capacity of single PDZ domains of PSD-95, one by one, and in combination, by structure-based amino acid replacements rather than domain deletion. Such a second-generation structure-function relation study surprisingly revealed that a quantitative binding between PSD-95 and synGAP tightly controlled the degree of PSD protein clustering in a manner that was inversely correlated with the distance from the spine head to the shaft. Thus, these results suggest the existence of a tight coordination between the state of PSD complex and the morphogenetic activity of each spine (Nonaka et al. J. Neurosci., 2006).

In parallel with this work, we and others determined that protein-protein interaction was key to determining the physical distance between the synaptic vesicles in the active zone and the voltage-gated calcium channels in its vicinity, the opening of which triggers their release (Kiyonaka et al., Nat. Neurosci. 2007).

Publications by lab members

(January 2022- December 2022)

1. Hamada S, Mikami K, Ueda S, Nagase M, Nagashima T, Yamamoto M, Bito H, Takemoto-Kimura S, Ohtsuka T, Watabe A. M. Experience-dependent changes in affective valence of taste in male mice. *Molecular Brain*, 16(1), 28, 2023, doi: 10.1186/s13041-023-01017-x
2. Ageta-Ishihara N, Takemoto-Kimura S, Kondo Y, Okamura M, Bito H. Lipidation states orchestrate CLICK-III/CaMKII γ 's stepwise association with Golgi and rafts-enriched membranes and specify its functional coupling to STEF-Rac1-dependent neurite extension, *Frontiers in Cellular Neuroscience*, 17: 1204302, 2023. doi: 10.3389/fncel.2023.1204302
3. Pagano R, Salamian A, Zielinski J, Beroun A, Nalberczak-Skóra M, Skonieczna E, Cały A, Tay N, Banaschewski T, Desrivières S, Grigis A, Garavan H, Heinz A, Brühl R, Martinot J.-L, Paillère Martinot M.-L, Artiges E, Nees F, Papadopoulos Orfanos D, Poustka L, Hohmann S, Fröhner J. H, Smolka M. N, Vaidya N, Walter H, Whelan R, IMAGEN consortium, Kalita K, Bito H, Müller C. P, Schumann G, Okuno H, Radwanska K. Arc controls alcohol cue relapse by a central amygdala mechanism. *Molecular Psychiatry*, 28, 733-745, 2023.

Neuroscience

2. Integrative Medical Neuroscience

Department of Child Neuropsychiatry

Associate Professor

Yukiko Kano, M.D., Ph.D.

Assistant Professor

Yu Hamamoto, M.D., Ph.D., Kouta Sasaki, M.D.

Homepage <http://childpsy.umin.jp/>

Introduction and Organization

Recently, mental problems of child and adolescent or problems of mental development are continuously increasing, and serious deficiency of specialists such as child psychiatrists and necessity of their development are emphasized. Especially, as Japan falls far behind other nations in research and education system of child psychiatry, development of specialists who can promote research by themselves and improve quality of diagnosis and treatment based on their own research are strongly demanded. In response to these needs, Department of Child Neuropsychiatry, Graduate School of Medicine was established in April 2010. This is believed to be the first Japanese department which works as an actual department of child psychiatry managed by child psychiatrist. Based on experience of clinical-based research as well as medical care and training of clinicians for decades in child psychiatry division of Department of Neuropsychiatry and Department of Child Psychiatry since April 2005, we are developing new activities. Professors are administrating Department of Child Psychiatry, the University Hospital also, and trying to utilize its clinical activities for research more effectively.

Teaching activities

In the year of 2023, we had 6 graduate students in doctor course. In addition to research training, educational program including case conference was

implemented with further improvement.

Research activities

Main subjects of our research are Autism Spectrum Disorder (ASD), Attention-Deficit/Hyperactivity Disorder (ADHD), Tourette syndrome which is a severe and chronic tic disorder, and child & adolescent obsessive-compulsive disorder (OCD). We are trying to combine scientific analysis of objective mental and behavioral indicators with neuropsychological, brain-imaging, and genetic studies into comprehensive and multidimensional approach to problems in development of brain and mind. We are applying this comprehensive approach to intervention studies including pharmacotherapy.

Major research projects with full or preliminary performance in 2023 are as follows:

- **Epidemiological, behavior phenotype, neuropsychological, and treatment study of Tourette syndrome (chronic tic disorder with multiple motor tics and one or more vocal tics) and child & adolescent OCD**

We are evaluating tics, obsessive-compulsive symptoms, and premonitory urges in Tourette syndrome and child & adolescent OCD to examine their relationship to each other, as well as investigating situation and needs for treatment and support to improve them.

We are following a clinical cohort of patients with

Tourette syndrome and are also investigating the impact of the COVID-19 pandemic. We are examining the neuropsychology of Tourette syndrome and the effectiveness of the Comprehensive Behavioral Intervention for Tics (CBIT). We have developed internet-based psychoeducational materials that will lead to CBIT, and are evaluating their effectiveness also.

Multi-institutional collaborative study about treatment-refractory Tourette syndrome in which severe tics persist even after adulthood are conducted with multidisciplinary professionals including neurosurgeons who perform deep brain stimulation.

We are also continuing to analyze the findings of our survey of tics and related behaviors in community preschoolers.

• **Brain-imaging study of ASD, ADHD and Tourette syndrome by structural-MRI, functional-MRI and near-infrared spectroscopy (NIRS)**

We continue to examine morphological and functional brain imaging in adults with ASD.

• **Development of predictor of parent training for ADHD**

We are examining what aspects of children with ADHD and their caregivers are affected by parent training. In addition to focusing on the relationship between parent training and attachment, we also aim to examine the relationship between brain function as measured by fMRI and these factors.

• **Effectiveness of psychological support for ASD**

We are examining effectiveness of early intervention for autistic preschoolers in terms of their communication behaviors and parental stress. We are also examining support for their transition from kindergarten and preschool to elementary school. Furthermore, effectiveness of a program of group cognitive behavior therapy for adults with high-functioning ASD is investigated in a randomized control trial.

• **Investigation on clinical evaluation and psychological education for adults with developmental disorders**

We are collecting and analyzing data obtained through

“inpatient assessment on developmental disorders” program, in which adult patients with suspected developmental disorders undergo detailed clinical assessment, including symptoms of ASD and ADHD, and receive psychoeducation based on this assessment.

References

1. Ishii-Takahashi A, Kawakubo Y, Hamada J, Nakajima N, Kawahara T, Hirose A, Yamaguchi R, Kuwabara H, Okada T, Kano Y. Changes in child behavioral problems and maternal attachment towards children with attention-deficit/hyperactivity disorder following behavioral parent training: A pilot study. *Psychiatry Clin Neurosci*, 77(7): 412-413, 2023.
2. Yamaguchi R, Kawahara T, Kotani T, Yazawa R, Suzuki A, Kano Y, Ishii-Takahashi A. The effectiveness of exercise programs accessible from home on children's and adolescents' emotional well-being: Systematic review & meta-analysis. *PCN Rep*, 2(2): e103, 2023.
3. Kageyama M, Yokoyama K, Ichihashi K, Noma S, Hashimoto R, Nishitani M, Okamoto R, Solomon P. A peer-led learning program about intimate and romantic relationships for persons with mental disorders (AIRIKI): co-creation pilot feasibility study. *BMC Psychiatry*, 23(1): 767, 2023.
4. Hasegawa N, Yasuda Y, Yasui-Furukori N, Yamada H, Hori H, Ichihashi K, Takaesu Y, Iida H, Muraoka H, Kodaka F, Iga JI, Hashimoto N, Ogasawara K, Ohi K, Fukumoto K, Numata S, Tsuboi T, Usami M, Hishimoto A, Furihata R, Kishimoto T, Nakamura T, Katsumoto E, Ochi S, Nagasawa T, Atake K, Kubota C, Komatsu H, Yamagata H, Ide K, Takeshima M, Kido M, Kikuchi S, Okada T, Matsumoto J, Miura K, Shimazu T, Inada K, Watanabe K, Hashimoto R. Effect of education regarding treatment guidelines for schizophrenia and depression on the treatment behavior of psychiatrists: A multicenter study. *Psychiatry Clin Neurosci*, 77(10): 559-568, 2023.
5. Hashimoto N, Yasui-Furukori N, Hasegawa N, Ishikawa S, Hori H, Iida H, Ichihashi K, Miura K, Matsumoto J, Numata S, Kodaka F, Furihata R,

- Ohi K, Ogasawara K, Iga JI, Muraoka H, Komatsu H, Takeshima M, Atake K, Kido M, Nakamura T, Kishimoto T, Hishimoto A, Onitsuka T, Okada T, Ochi S, Nagasawa T, Makinodan M, Yamada H, Tsuboi T, Yamada H, Inada K, Watanabe K, Hashimoto R. Change of prescription for patients with schizophrenia or major depressive disorder during admission: real-world prescribing surveys from the effectiveness of guidelines for dissemination and education psychiatric treatment project. *BMC Psychiatry*, 23(1): 473, 2023.
6. Onitsuka T, Okada T, Hasegawa N, Tsuboi T, Iga JI, Yasui-Furukori N, Yamada N, Hori H, Muraoka H, Ohi K, Ogasawara K, Ochi S, Takeshima M, Ichihashi K, Fukumoto K, Iida H, Yamada H, Furihata R, Makinodan M, Takaesu Y, Numata S, Komatsu H, Hishimoto A, Kido M, Atake K, Yamagata H, Kikuchi S, Hashimoto N, Usami M, Katsumoto E, Asami T, Kubota C, Matsumoto J, Miura K, Hirano Y, Watanabe K, Inada K, Hashimoto R. Combination Psychotropic Use for Schizophrenia With Long-Acting Injectable Antipsychotics and Oral Antipsychotics: A Nationwide Real-World Study in Japan. *J Clin Psychopharmacol*, 43(4): 365-368, 2023.

Neuroscience

3. Clinical Neuroscience

Department of Neuropsychiatry

Professor

Kiyoto Kasai, M.D., Ph.D.

Associate Professor

Seiichiro Jinde, M.D., Ph.D.

Shuntaro Ando, M.D., Ph.D.

Lecturer

Shinsuke Kondo, M.D., Ph.D.

Kayo Ichihashi, M.D., Ph.D.

Eisuke Sakakibara, M.D., Ph.D.

Research Associate

Shinya Fujikawa, M.D., Ph.D.

Tempei Ikegame, M.D., Ph.D.

Daisuke Koshiyama, M.D., Ph.D.

Yosuke Kumakura, M.D.

Mizuo Hoshino, M.D., Ph.D.

Akiko Kanehara, Ph.D.

Susumu Morita, M.D., Ph.D.

Tatsuro Asai, M.D., Ph.D.

Masashi Mizutani, M.D., Ph.D.

Homepage <http://npsy.umin.jp/>

Introduction and Organization

The Department of Neuropsychiatry is the oldest department of psychiatry in Japan which was established in 1886. "Anti-Psychiatry" movement in the last 3 decades had brought highly negative impacts on the progress of all aspects of our activities. However, in 1994, our department has been normalized and restarted to play a leading role in psychiatry in Japan. Since 2005, we have launched the new department of child neuropsychiatry to focus on basic and clinical neuroscience in the developmental disorders including autism spectrum disorder (ASD). Dr. Kiyoto Kasai has been serving as a professor since 2008. Now the Department of Neuropsychiatry is dedicated to high quality clinical services, excellent training, education for students and innovative research.

staff psychiatrists, 5 clinical psychologists and 2 psychiatric social workers. In 2023, 655 new patients visited our outpatient clinic, and the total visits per day were about 100.

In our inpatient wards, the secluded ward has 27 beds including 3 seclusion rooms, as well as 21 beds for the open general ward. 351 patients with various psychiatric disorders were admitted in 2023. Recently, the number of inpatients who were referred from the emergency unit is increasing. Mean hospitalization is 30 day long, and the age of patients is from teenager to senior. Most of the patients are schizophrenia, mood disorder and the psychosis based on the somatic diseases. Modified electro-convulsive therapy was performed for more than 200 times per year.

We established the day care unit for outpatients with schizophrenia in 1974, and the patients are engaged in rehabilitation and re-work programs.

Clinical activities

For our clinical services, we have more than 15

Education

For psychiatric residents, we have provided: 1) clinical meetings on patients (every morning); 2) case conferences on inpatients (every week); 3) a series of lectures by teaching staffs on various aspects of psychiatry. For undergraduates, we have provided neuropsychiatry comprehensive lectures (for 2nd year students), and clinical clerkship (for 3rd year students). For postgraduate, currently more than 10 neuropsychiatry Ph.D. students are studying.

Research

Our mission in research is to clarify the pathophysiology of the mental illness to develop better treatment approach.

1) Neuroimaging

Our research plays a leading role in psychiatric neuroimaging in Japan and aims at multi-modality neuroimaging (structural and functional MRI, MR spectroscopy, EEG, MEG, near-infrared spectroscopy (NIRS)) in schizophrenia, mood disorders and autism spectrum disorders.

2) Molecular/cellular neuroscience

The goal of the molecular/cellular neuroscience group is to build causal bridges among the molecular, cellular, neural systems, and behavior on the rodent model of neuropsychiatric disorders. We employ integrated multidisciplinary techniques including genetics, cell biology, biochemistry, histology, electrophysiology, imaging, and behavioral analysis for elucidating molecular pathophysiology of rodent models of neuropsychiatric disorder. We have focused on schizophrenia and hippocampal neuronal circuits.

3) Genetic and Epidemiology research

The Genetic Research Group of the department is investigating genetic as well as environmental mechanism of psychiatric disorders. A major focus of the studies is exploration of susceptibility genes of the disorders including schizophrenia, autism, their spectrum disorders and anxiety disorder (mainly panic disorder).

Publications

1. Furukawa Y, Luo Y, Funada S, Onishi A, Ostinelli E, Hamza T, Furukawa TA, Kataoka Y. Optimal duration of antibiotic treatment for community-acquired pneumonia in adults: a systematic review and duration-effect meta-analysis. *BMJ Open*. 2023 Mar 22;13(3):e061023.
2. Morishima R, Kanehara A, Aizawa T, Okada N, Usui K, Noguchi H, Kasai K: Long-Term Trends and Sociodemographic Inequalities of Emotional/Behavioral Problems and Poor Help-Seeking in Adolescents During the COVID-19 Pandemic. *J Adolesc Health*. 2024;74(3):537-544.
3. Morita M, Ando S, Kiyono T, Morishima R, Yagi T, Kanata S, Fujikawa S, Yamasaki S, Nishida A, Kasai K: Bidirectional relationship of problematic Internet use with hyperactivity/inattention and depressive symptoms in adolescents: a population-based cohort study. *Eur Child Adolesc Psychiatry*. 2022 Oct;31(10):1601-1609.
4. Oguro S, Echizen K, Sakakibara E, Koshiyama D, Oji T, Miyake T, Kasai K. Clozapine-induced pemphigus successfully treated with methylprednisolone pulse without discontinuation of clozapine: a case report. *Psychiatry Clin Neurosci*. 2023 Oct;77(10):572-573.
5. Okada N, Fukunaga M, Miura K, Nemoto K, Matsumoto J, Hashimoto N, Kiyota M, Morita K, Koshiyama D, Ohi K, Takahashi T, Koeda M, Yamamori H, Fujimoto M, Yasuda Y, Hasegawa N, Narita H, Yokoyama S, Mishima R, Kawashima T, Kobayashi Y, Sasabayashi D, Harada K, Yamamoto M, Hirano Y, Itahashi T, Nakataki M, Hashimoto RI, Tha KK, Koike S, Matsubara T, Okada G, van Erp TGM, Jahanshad N, Yoshimura R, Abe O, Onitsuka T, Watanabe Y, Matsuo K, Yamasue H, Okamoto Y, Suzuki M, Turner JA, Thompson PM, Ozaki N, Kasai K, Hashimoto R. Subcortical volumetric alterations in four major psychiatric disorders: a mega-analysis study of 5604 subjects and a volumetric data-driven approach for classification. *Mol Psychiatry*. 2023 Aug 4.
6. Sakakibara, E. Epistemic injustice in the therapeutic relationship in psychiatry. *Theoretical Medicine and Bioethics* 2023 May 24; 44,

- 477-502.
7. Tada M, Kirihara K, Koshiyama D, Nagai T, Fujioka M, Usui K, Satomura Y, Koike S, Sawada K, Matsuoka J, Morita K, Araki T, Kasai K. Alterations of auditory-evoked gamma oscillations are more pronounced than alterations of spontaneous power of gamma oscillation in early stages of schizophrenia. *Transl Psychiatry*. 2023 Jun 27; 13(1):218.
 8. Tada M, Kirihara K, Nagai T, Koike S, Araki T, Kasai K: Gamma-band harmonic responses for beta-band auditory steady-state response are intact in patients with early stage schizophrenia. *Neuropsychopharm Rep*. 2024 Mar;44(1):240-245. Epub 2023 Nov 27.
 9. Usui K, Kirihara K, Araki T, Tada M, Koshiyama D, Fujioka M, Nishimura R, Ando S, Koike S, Sugiyama H, Shirakawa T, Toriyama R, Masaoka M, Fujikawa S, Endo K, Yamasaki S, Nishida A, Kasai K. Longitudinal change in mismatch negativity (MMN) but not in gamma-band auditory steady-state response (ASSR) is associated with psychological difficulties in adolescence. *Cereb Cortex*. 2023 Nov 4;33(22):11070-11079.
 10. Yamaguchi S, Ando S, Miyashita M, Usami S, Yamasaki S, Endo K, DeVyllder J, Stanyon D, Baba K, Nakajima N, Niimura J, Nakanishi M, Hiraiwa-Hasegawa M, Kasai K, Nishida A. Longitudinal relationships between help-seeking intentions and depressive symptoms in adolescents. *J Adolesc Health*. 2023 Sep 4:S1054-139X(23)00347-6.
 11. Kasai K, Kumagaya S, Takahashi Y, Sawai Y, Uno A, Kumakura Y, Yamagishi M, Kanehara A, Morita K, Tada M, Satomura Y, Okada N, Koike S, Yagishita S: "World-Informed" neuroscience for diversity and inclusion: An organizational change in cognitive sciences. *Clin EEG Neurosci* 54: 560-566, 2023.

Department of Neurology

Professor

Tatsushi Toda, M.D., Ph.D.

Associate Professor

Wataru Satake, M.D., Ph.D.

Lecturer

Masashi Hamada, M.D., Ph.D.

Akatsuki Kubota, M.D., Ph.D.

Associate

Meiko Maeda, M.D., Ph.D., Takashi Matsukawa, M.D., Ph.D.,

Satoshi Kodama, M.D., Ph.D., Toshiyuki Kakumoto M.D., Ph.D., Atsushi Sudo M.D., Ph.D.

Homepage <http://www.utokyo-neurology.org>

Introduction and Organization

The Department of Neurology was established by the founder Professor Yasuo Toyokura in 1964 as one Department in the Brain Research Institute. The Department of Neurology was succeeded by Professors Toru Mannen, Ichiro Kanazawa, and Shoji Tsuji. The organization of the Brain Research Institute was reorganized as the Division of Neuroscience of the Graduate School of Medicine in 1997.

Clinical activities

We offer clinical services in the field of Neurology. We are putting our effort to provide the patients with highly advanced clinical practice as well as on clinical activities connected to postgraduate education of Neurology.

We have outpatient clinics covering the broad fields of Neurology. Furthermore, we also provide clinics specialized to movement disorders, dementia (Dementia center), multiple system atrophy, adrenoleukodystrophy, epilepsy, neuroimmunology, neuromuscular disorders, and headaches.

In the in-patient ward, we offer programs for postgraduate education including the program for the

first stage postgraduate education. We also offer the excellent training program with the goal to get the board of Neurologist. In 2005, we initiated deep brain stimulation for the treatment of movement disorders in cooperation with Department of Neurosurgery.

Teaching activities

As for under-graduate education, our Department takes a part in lectures of Neurology for the 4th and 5th grade medical students, and clinical clerkship for the 5th grade medical students.

In the clinical clerkship we include small group lectures including neurological examination, neurophysiology, and stroke care. We are also putting our effort for Free Quarters where we offer various opportunities for medical students to be involved in research activities, and 2-3 medical students are conducting their research activities in the laboratories.

In postgraduate education we offer the integrated program including Neurology as the part of the program of Internal Medicine.

Regarding training for board-certified neurologists, we offer the excellent program including patients' care, training in Neurophysiology and Neuro-

pathology, consultation for Neurology and supervising of junior trainees. This program is integrated with clinical practice at the affiliated hospitals where rich experience is obtained for numerous cases in Clinical Neurology.

In Graduate School, we offer highly advanced research activities based on the interest of graduate students.

Research activities

Our research field covers broad fields related to neurological diseases, with the goals to elucidate the mechanisms of neurological diseases, and to eventually develop new therapeutic strategies. Our research activities include molecular genetics, developmental biology, cell biology, pharmacology, pathology, and physiology. We aim to integrate these broad research fields to better contribute to clinical neurology.

In the development of molecular therapeutics that ameliorate α -dystroglycan (α -DG)-associated diseases, we identified the glycan unit ribitol 5-phosphate (Rbo5P) in α -DG and showed that enzyme activities of α -DG-associated diseases are involved in the synthesis of tandem Rbo5P. We also found that FKTN and FKRP can transfer GroP to O-mannosyl glycans by using CDP-glycerol (CDP-Gro) as a donor substrate. The analysis of mouse models of α -DG-associated diseases indicated that spatiotemporal persistence of functionally glycosylated α -DG may be crucial for brain development. These findings provide insight into pathogenesis and therapeutic strategies in α -DG-associated diseases. In addition, a First In Human clinical trial of a novel antisense nucleic acid NS-035 in Fukuyama-type congenital muscular dystrophy, which is common in Japan due to dystroglycanopathy is currently underway. (Toda, T., Kanagawa, M., Kobayashi, K., Sudo, A., Fujino, G., Maeda, M., Takahashi, A.)

We perform case-control association studies in Parkinson disease (PD) employing whole-exome sequence analysis to discover rare PD susceptibility variants. Employing a novel bioinformatics approach using GWAS loci in PD along with in vitro functional studies and MPTP mouse model analysis, we identified a novel drug candidate for the prevention of neurodegeneration in PD. We also identified genetic

factors responsible for the individual difference of the effects of zonisamide by using GWAS and transcriptome analysis. (Toda, T., Satake, W., Uenaka, T., Cha, P.C., Fujino, G., Naito, T.)

In the field of molecular genetics, we have developed the Genomic Medicine Research Support Center, and introduced next-generation sequencers to conduct comprehensive genome analyses to elucidate molecular bases of various neurological diseases. Regarding monogenic neurologic diseases, we conduct pedigree analyses in various neurological diseases including epilepsy, multiple system atrophy, amyotrophic lateral sclerosis, hereditary spastic paraplegia, spinocerebellar ataxia, and adrenoleukodystrophy. As for sporadic neurologic diseases, we perform case-control association studies in multiple system atrophy and amyotrophic lateral sclerosis to identify genetic factors underlying these diseases. On the basis of the findings that mutations in *COQ2* are associated with familial as well as sporadic multiple system atrophy, we are conducting an investigator-initiated clinical trial using coenzyme Q10 for patients with multiple system atrophy. Genetic study on benign adult familial myoclonus epilepsy (BAFME), neuronal intranuclear inclusion disease (NIID), oculopharyngeal myopathy with leukoencephalopathy (OPML), and oculopharyngodistal myopathy type 1 (OPDM1) are performed, which have been revealed to be caused by expansions of noncoding repeats at our department. We reported safety and efficacy of hematopoietic stem cell transplantation for adolescent/adulthood-onset cerebral form/cerebello-brainstem form of adrenoleukodystrophy. We are now studying a biomarker for adrenoleukodystrophy. (Toda, T., Tsuji, S., Mitsui, J., Matsukawa, T., Naruse, H., Kakumoto, T., Mitsutake, A., Yamaguchi, N., Porto, K. J. L., Orimo, K.)

The human neurophysiology section specializes in studying the physiology of the human motor and sensory systems in awake healthy volunteers and the pathophysiology of neurological disorders using several non-invasive physiological methods, such as TMS, EEG, MEG, fMRI, NIRS and EOG. Our final goal is to devise new therapeutic techniques for intractable neurological disorders. To this end, the work extends from the study of spinal systems to basal ganglia and cerebral cortex. We are interested in

sensor-oriented and sensor-free motion measurements in Parkinson disease, network analysis in patient with epilepsy using MEG, fMRI of spinal cord and neuronal excitability changes in dystonic patients. To this end. (Hamada, M., Shiota, Y., Kodama, S., Katsuse K, Tokimura R, Miyano R., Kotani R., Kimura T.)

In the field of neuromuscular diseases, we provide pathological diagnosis of biopsied materials from patients with myopathy or neuropathy. We also provide autoantibody testing for anti-ganglioside antibodies, and muscle specific antibodies. In research field, using biopsied muscles and collected serum samples, we have been studying the mechanisms of inflammatory myopathies from the viewpoints of pathological changes, myositis specific autoantibodies, serum cytokines, and expression profiling of muscle samples. Our aim is to increase understanding of the etiology and pathogenesis of neuromuscular diseases. (Kubota A., Maeda M., Kitamura A., Komaki S., Shimizu, J.).

Neuroimmunology section is focused on understanding inflammatory disease of the CNS: namely multiple Sclerosis and neuromyelitis optica. Through application of both conventional and more contemporary immunological methods (FACS, ELISA, cell culture and NGS analysis), we aim to reveal disease-specific patho-mechanisms for better diagnosis and treatment of immune-mediated CNS inflammation. (Sakuishi K, Koguchi A, and Kawasaki R)

Publication

1. Teranishi Y, Miyawaki S, Nakatochi M, Okano A, Ohara K, Hongo H, Ishigami D, Sakai Y, Shimada D, Takayanagi S, Ikemura M, Komura D, Katoh H, Mitsui J, Morishita S, Ushiku T, Ishikawa S, Nakatomi H, Saito N. Meningiomas in patients with neurofibromatosis type 2 predominantly comprise 'immunogenic subtype' tumours characterised by macrophage infiltration.
2. Orimo K, Kakumoto T, Hara R, Goto R, Ishiura H, Mitsui J, Yoshida C, Uesaka Y, Suzuki Y, Morishita S, Satake W, Tsuji S, Toda T. A Japanese family with idiopathic basal ganglia calcification carrying a novel XPR1 variant. *J Neurol Sci.* 2023 Aug 15;451:120732. doi: 10.1016/j.jns.2023.120732.
3. Nakahara Y, Mitsui J, Date H, Porto KJ, Hayashi Y, Yamashita A, Kusakabe Y, Matsukawa T, Ishiura H, Yasuda T, Iwata A, Goto J, Ichikawa Y, Momose Y, Takahashi Y, Toda T, Ohta R, Yoshimura J, Morishita S, Gustavsson EK, Christy D, Maczis M, Farrer MJ, Kim HJ, Park SS, Jeon B, Zhang J, Gu W, Scholz SW, Singleton AB, Houlden H, Yabe I, Sasaki H, Matsushima M, Takashima H, Kikuchi A, Aoki M, Hara K, Kakita A, Yamada M, Takahashi H, Onodera O, Nishizawa M, Watanabe H, Ito M, Sobue G, Ishikawa K, Mizusawa H, Kanai K, Kuwabara S, Arai K, Koyano S, Kuroiwa Y, Hasegawa K, Yuasa T, Yasui K, Nakashima K, Ito H, Izumi Y, Kaji R, Kato T, Kusunoki S, Osaki Y, Horiuchi M, Yamamoto K, Shimada M, Miyagawa T, Kawai Y, Nishida N, Tokunaga K, Dürr A, Brice A, Filla A, Klockgether T, Wüllner U, Tanner CM, Kukull WA, Lee VM, Masliah E, Low PA, Sandroni P, Ozelius L, Foroud T, Tsuji S. Genome-wide association study identifies a new susceptibility locus in PLA2G4C for Multiple System Atrophy. *medRxiv [Preprint]*. 2023 May 2:2023.05.02.23289328. doi: 10.1101/2023.05.02.23289328.
4. Mitsui J, Matsukawa T, Uemura Y, Kawahara T, Chikada A, Porto KJL, Naruse H, Tanaka M, Ishiura H, Toda T, Kuzuyama H, Hirano M, Wada I, Ga T, Moritoyo T, Takahashi Y, Mizusawa H, Ishikawa K, Yokota T, Kuwabara S, Sawamoto N, Takahashi R, Abe K, Ishihara T, Onodera O, Matsuse D, Yamasaki R, Kira JI, Katsuno M, Hanajima R, Ogata K, Takashima H, Matsushima M, Yabe I, Sasaki H, Tsuji S. High-dose ubiquinol supplementation in multiple-system atrophy: a multicentre, randomised, double-blinded, placebo-controlled phase 2 trial. *EClinicalMedicine.* 2023 Apr 14;59:101920. doi: 10.1016/j.eclinm.2023.101920.
5. Naruse H, Okubo S, Sudo A, Mitsui J, Mikata T, Ishiura H, Morishita S, Tsuji S, Toda T. Clinical features of a family with late-onset distal hereditary motor neuropathy harboring p.Pro39Leu variant of HSPB1. *J Peripher Nerv Syst.* 2023 Sep;28(3):518-521. doi: 10.1111/jns.12567.
6. Kuroda Y, Saito Y, Enomoto Y, Naruto T, Mitsui J,

- Kurosawa K. PHACES-like syndrome with TMEM260 compound heterozygous variants. *Am J Med Genet A*. 2023 Aug;191(8):2215-2218. doi: 10.1002/ajmg.a.63245.
7. Kawamoto N, Hamada Y, Kobayashi S, Naruse H, Ishiura H, Matsukawa T, Mitsui J, Tsuji S, Sonoo M, Toda T. Noncanonical splice-site variant in peripheral myelin protein 22 gene (PMP22) in a patient with hereditary neuropathy with liability to pressure palsies. *J Peripher Nerv Syst*. 2023 Sep;28(3):513-517. doi: 10.1111/jns.12558.
 8. Mitsutake A, Matsukawa T, Iwata A, Ishiura H, Mitsui J, Mori H, Toya T, Honda A, Kurokawa M, Sakai N, Tsuji S, Toda T. Favorable outcome of hematopoietic stem cell transplantation in late-onset Krabbe disease. *Brain Dev*. 2023 Aug; 45(7):408-412. doi: 10.1016/j.braindev.2023.04.001.
 9. Takegami N, Mitsutake A, Mano T, Shintani-Domoto Y, Unuma A, Yamaguchi-Takegami N, Ishiura H, Sakuishi K, Ando M, Yamauchi H, Ono M, Morishita S, Mitsui J, Shimizu J, Tsuji S, Toda T. The Myocardial Accumulation of Aggregated Desmin Protein in a Case of Desminopathy with a de novo DES p.R406W Mutation. *Intern Med*. 2023 Oct 1;62(19):2883-2887. doi: 10.2169/internalmedicine.0992-22.
 10. Hama Y, Date H, Fujimoto A, Matsui A, Ishiura H, Mitsui J, Yamamoto T, Tsuji S, Mizusawa H, Takahashi Y. A Novel de novo KIF1A Mutation in a Patient with Ataxia, Intellectual Disability and Mild Foot Deformity. *Cerebellum*. 2023 Dec; 22(6):1308-1311. doi: 10.1007/s12311-022-01489-y.
 11. Ueda M, Katsuse K, Kakumoto T, Kobayashi S, Ishiura H, Mitsui J, Toda T. Copper Deficiency in Wilson's Disease with a Normal Zinc Value. *Intern Med*. 2023 Apr 1;62(7):1073-1076. doi: 10.2169/internalmedicine.9366-22.
 12. Hongo H, Miyawaki S, Teranishi Y, Mitsui J, Katoh H, Komura D, Tsubota K, Matsukawa T, Watanabe M, Kurita M, Yoshimura J, Dofuku S, Ohara K, Ishigami D, Okano A, Kato M, Hakuno F, Takahashi A, Kunita A, Ishiura H, Shin M, Nakatani H, Nagao T, Goto H, Takahashi SI, Ushiku T, Ishikawa S, Okazaki M, Morishita S, Tsuji S, Saito N. Somatic GJA4 gain-of-function mutation in orbital cavernous venous malformations. *Angiogenesis*. 2023 Feb;26(1):37-52. doi: 10.1007/s10456-022-09846-5.
 13. Egashira S, Shin JH, Yoshimura S, Koga M, Ihara M, Kimura N, Toda T, Imanaka Y. Cost-effectiveness of endovascular therapy for acute stroke with a large ischemic region in Japan: impact of the Alberta Stroke Program Early CT Score on cost-effectiveness. *J Neurointerv Surg*. 2023 Dec 10;jnis-2023-021068. doi: 10.1136/jnis-2023-021068.
 14. Nakamura R, Tomizawa I, Iwai A, Ikeda T, Hirayama K, Chiu YW, Suzuki T, Tarutani A, Mano T, Iwata A, Toda T, Sohma Y, Kanai M, Hori Y, Tomita T. Photo-oxygenation of histidine residue inhibits α -synuclein aggregation. *FASEB J*. 2023 Dec;37(12):e23311. doi: 10.1096/fj.202301533R.
 15. Li D, Johmura Y, Morimoto S, Doi M, Nakanishi K, Ozawa M, Tsunekawa Y, Inoue-Yamauchi A, Naruse H, Matsukawa T, Takeshita Y, Suzuki N, Aoki M, Nishiyama A, Zeng X, Konishi C, Suzuki N, Nishiyama A, Harris AS, Morita M, Yamaguchi K, Furukawa Y, Nakai K, Tsuji S, Yamazaki S, Yamanashi Y, Shimada S, Okada T, Okano H, Toda T, Nakanishi M. LONRF2 is a protein quality control ubiquitin ligase whose deficiency causes late-onset neurological deficits. *Nat Aging*. 2023 Aug;3(8):1001-1019. doi: 10.1038/s43587-023-00464-4.
 16. Kakumoto T, Matsukawa T, Ishiura H, Mori H, Tsuji S, Toda T. Neurofilament light chain levels in cerebrospinal fluid as a sensitive biomarker for cerebral adrenoleukodystrophy. *Ann Clin Transl Neurol*. 2023 Jul;10(7):1230-1238. doi: 10.1002/acn3.51818.
 17. Tokushige SI, Matsumoto H, Matsuda SI, Inomata-Terada S, Kotsuki N, Hamada M, Tsuji S, Ugawa Y, Terao Y. Early detection of cognitive decline in Alzheimer's disease using eye tracking. *Front Aging Neurosci*. 2023 Mar 21;15:1123456. doi: 10.3389/fnagi.2023.1123456.
 18. Nakatani-Enomoto S, Hanajima R, Hamada M, Matsumoto H, Terao Y, Jun Groiss S, Murakami T, Abe M, Enomoto H, Kawai K, Kan R, Niwa SI, Yabe H, Ugawa Y. Quadripulse transcranial magnetic stimulation inducing long-term depres-

- sion in healthy subjects may increase seizure risk in some patients with intractable epilepsy *Clin Neurophysiol Pract.* 2023 Jul 7;8:137-142. doi: 10.1016/j.cnp.2023.07.001.
19. Inomata-Terada S, Fukuda H, Tokushige SI, Matsuda SI, Hamada M, Ugawa Y, Tsuji S, Terao Y. Abnormal saccade profiles in hereditary spinocerebellar degeneration reveal cerebellar contribution to visually guided saccades. *Clin Neurophysiol.* 2023 Oct;154:70-84. doi: 10.1016/j.clinph.2023.07.006. Epub 2023 Jul 31.
 20. Kodama S, Jo T, Yasunaga H, Ohbe H, Michihata N, Matsui H, Okada A, Shiota Y, Fushimi K, Toda T, Hamada M. Perioperative Use of Intravenous Levodopa as an Anti-Parkinsonian Drug: A Propensity Score Analysis. *Mov Disord Clin Pract.* 2023 Oct 13;10(11):1650-1658. doi: 10.1002/mdc3.13894.
 21. Shiota Y, Fushimi M, Sekino M, Yumoto M. Investigating the technical feasibility of magnetoencephalography during transcranial direct current stimulation. *Front Hum Neurosci.* 2023 Sep 13;17:1270605. doi: 10.3389/fnhum.2023.1270605.
 22. Ma K, Hamada M, Di Lazzaro V, Hand B, Guerra A, Opie GM, Goetz SM. Correlating active and resting motor thresholds for transcranial magnetic stimulation through a matching model. *Brain Stimul.* 2023 Nov-Dec;16(6):1686-1688. doi: 10.1016/j.brs.2023.11.009.
 23. Hatano K, Orimo K, Ogura M, Okabe S, Ishida T, Kubota A, Shimizu J, Hashida H. Development of Polyneuropathy, Organomegaly, Endocrinopathy, M Protein, and Skin Changes Syndrome after Conversion from Plasmacytoma of Bone to Multiple Myeloma. *Intern Med.* 2023; 62: 475-479.
 24. Egashira S, Kubota A, Kakumoto T, Kawasaki R, Kotani R, Sakuishi K, Iwata A, Bae SK, Akamatsu N, Hasegawa K, Tanaka M, Nakamichi K, Saijo M, Toda T. Long-term survival from progressive multifocal leukoencephalopathy in living-donor liver transplant recipient with preformed donor-specific antibody. *J Neurovirol.* 2023; 29: 519-523.
 25. Aiba I, Hayashi Y, Shimohata T, Yoshida M, Saito Y, Wakabayashi K, Komori T, Hasegawa M, Ikeuchi T, Tokumaru AM, Sakurai K, Murayama S, Hasegawa K, Uchihara T, Toyoshima Y, Saito Y, Yabe I, Tanikawa S, Sugaya K, Hayashi K, Sano T, Takao M, Sakai M, Fujimura H, Takigawa H, Adachi T, Hanajima R, Yokota O, Miki T, Iwasaki Y, Kobayashi M, Arai N, Ohkubo T, Yokota T, Mori K, Ito M, Ishida C, Tanaka M, Idezuka J, Kanazawa M, Aoki K, Aoki M, Hasegawa T, Watanabe H, Hashizume A, Niwa H, Yasui K, Ito K, Washimi Y, Mukai E, Kubota A, Toda T, Nakashima K. Clinical course of pathologically confirmed corticobasal degeneration and corticobasal syndrome. *Brain Commun.* 2023; 5: fcad296.
 26. Uchio N, Komaki S, Sudo T, Matsumoto Y, Hao A, Kojima K, Toda N, Kitamura A, Maeda MH, Kubota A, Matsumoto H. Anti-nuclear matrix protein 2 antibody-positive dermatomyositis with gastrointestinal ulcers: A case report. *Int J Rheum Dis.* 2023; 26: 2572-2575.
 27. Ishiura H, Tsuji S, Toda T, Recent advances in CGG repeat diseases and a proposal of fragile X-associated tremor/ataxia syndrome, neuronal intranuclear inclusion disease, and oculopharyngodistal myopathy (FNOP) spectrum disorder. *J Hum Genet.* 2023;68(3):169-174. doi:10.1038/s10038-022-01116-y
 28. Nakashima S, Hamada M, Kimura T, Tanifuji S, Takahashi A, Yashita D, Kakimoto Y, Matsukawa T, Ishiura H, Toda T. Case Report: Intraventricular Cerliponase Alfa Treatment in a Patient with Advanced Neuronal Ceroid Lipofuscinosis Type 2. *Intern Med.* 2024;63(12): 1807-1812.
 29. Takegami N, Murai H, Mori H, Yamaguchi-Takegami N, Toda T, Iwata NK, Goto J. Multiple cortical lesions with grainy enhancement of magnetic resonance imaging in anti-myelin oligodendrocyte glycoprotein (MOG) antibody-associated encephalitis with seizures (FLAMES). *J Neurol Sci.* 2023;451:120729.
 30. Yamakawa K, Nishijima H, Kubota A, Naruse H, Baba S, Fujimaki Y, Kondo K, Toda T, Yamasoba T. Clinical and electrophysiological findings of facial palsy in a case of hereditary gelsolin amyloidosis. *Auris Nasus Larynx.* 2023;50(2): 305-308.
 31. Enkhjargal S, Sugahara K, Khaledian B,

- Nagasaka M, Inagaki H, Kurahashi H, Koshimizu H, Toda T, Taniguchi-Ikeda M. Antisense oligonucleotide induced pseudoexon skipping and restoration of functional protein for Fukuyama muscular dystrophy caused by a deep-intronic variant. *Hum Mol Genet.* 2023; 32(8):1301-1312.
32. Kurihara M, Mano T, Eto F, Yao I, Sato K, Ohtomo G, Bannai T, Shibata S, Ishiura H, Ikemura M, Matsubara T, Morishima M, Saito Y, Murayama S, Toda T, Setou M, Iwata A. Proteomic profile of nuclei containing p62-positive inclusions in a patient with neuronal intranuclear inclusion disease. *Neurobiol Dis.* 2023;177:105989.
33. Masuzawa H, Suzuki F, Amemiya S, Orimo K, Ishiura H, Hara R, Toda T, Nakazawa T, Honda A, Tanaka M, Hinata M, Abe O. A case of intravascular lymphoma presenting with a lesion in the splenium of the corpus callosum. *Radiol Case Rep.* 2023;18(5):1929-1932.

Department of Neurosurgery

Professor

Nobuhito Saito, M.D., Ph.D.

Associate Professor

Satoru Miyawaki, M.D., Ph.D.

Lecturer

Shunsaku Takayanagi, M.D., Ph.D.

Assistant Professor

Hirokazu Takami, M.D., Ph.D.

Masashi Nomura, M.D., Ph.D.

Seijiro Shimada, M.D., Ph.D.

Naoyuki Shono, M.D., Ph.D.

Satoshi Koizumi, M.D.

Hiroataka Hasegawa, M.D., Ph.D.

Satoshi Kiyofuji, M.D., Ph.D.

Hiroki Hongo, M.D., Ph.D.

Keisuke Nagata, M.D., Ph.D.

Motoyuki Umekawa, M.D.

Specially Appointed Associate Professor at Medical Information Engineering

Taichi Kin, M.D., Ph.D.

Homepage <http://www.h.u-tokyo.ac.jp/neurosurg/>

Introduction and Organization

The Department of Neurosurgery at the University of Tokyo Hospital consists of 14 staff neurosurgeons, who participate in the three major academic activities: patient care, research, and education. The staffs include a professor/chairman, three lecturers, ten assistant professors and one project associate professor at Medical Information Technology.

Clinical ward for neurosurgery in our university hospital was founded in 1951 as the first neurosurgical clinic in Japan. Dr. Keiji Sano, as the founding professor, established the Department of Neurosurgery in 1962. Dr. Kintomo Takakura and Dr. Takaaki Kirino served as the second and the third professor, respectively. The incumbent professor, Dr. Nobuhito Saito, has been serving as the fourth professor since 2006.

Our department provides expertise for patients with brain tumor, cerebrovascular disease, spinal disease, functional disorder, head trauma, etc.

Clinical activities

General outpatient clinic including new patient clinic is open every weekday and subspecialty clinic is open three days a week (Monday and Friday). The latter is open for patients with brain tumor, pituitary disease, spinal disease, cerebrovascular disease, endovascular intervention, epilepsy, and gamma knife treatment. From April 2023 to March 2024, 18,320 patients were treated at the outpatient clinics.

The neurosurgery ward has approximately 40 beds on the seventh floor of the hospital building opened in September 2001. In 2023, 969 patients were admitted to the neurosurgery ward. 470 surgical procedures and 191 gamma knife procedures were performed in 2023.

Our practice covers a wide variety of neurosurgical diseases including malignant and benign brain tumors, hemorrhagic and thromboembolic cerebrovascular diseases, spinal disorders, pediatric diseases, epilepsy, pain and movement disorders.

Intraoperative functional monitoring in brain tumor surgery and pre- and intra-operative functional mapping in epilepsy surgery are frequently used to preserve brain function as much as possible. Endoscopic endonasal surgery is also frequently utilized as a minimally invasive therapeutic option for skull base lesions. An endoscopic approach to intraventricular lesions, as well as cystic lesions in pediatric patients, is commonly employed by neuroendoscope specialists, which is another advantage of our facility. State-of-the-art techniques including intraoperative computer-aided navigation and intravascular procedures help our continuous effort to increase the safety of surgical treatment. Some endovascular procedures are performed in our hybrid operating room with the cooperation of the operation department and the anesthesiology doctors.

Our department is affiliated with 32 neurosurgical institutions in and around the city of Tokyo including 10 university medical centers, where our residents and students are exposed to various clinical experiences. Surgical case volume in all hospitals exceeds 11,600 cases.

Teaching activities

Medical students take lectures of clinical neurosurgery in their second year. Clinical case studies and bedside teaching are scheduled in the third and fourth years. The lecturers introduce general neurosurgery as well as the state-of-art neurosurgical practice to the students. At the bedside teaching and clinical clerkship, they are offered opportunities to learn clinical management of neurosurgical patients in the hands-on style, and also are exposed to practice in various subspecialties in neurosurgery through special seminars given by experts in the fields.

We accepted 7 in 2021, 12 in 2022, and 4 in 2023 in our neurosurgical residency program. These residents are trained in the university hospital and affiliated hospitals to experience every aspect of neurosurgical practice for five years on average. Our residency

training is finalized after the sixth year, when the finishing residents serve as senior residents at the university hospital for 6 months. Academic training is provided through numerous intramural clinical and research conferences, journal clubs, seminars as well as quarterly regional meetings of the Japan Neurosurgical Society. After or during residency training, our residents can choose to be admitted into the Ph.D. course at the Graduate School of Medicine, the University of Tokyo, to be involved in advanced basic research activities for 4 years. Upon completion of training, our graduates stay in the department to be associates in our university hospital or become clinical staffs in our affiliated hospitals.

Research activities

Clinical research in the last few years have mainly focused on treatments of acoustic neurinoma, techniques of skull base surgery, treatments of malignant brain tumors, epilepsy surgery, and stereotactic radiosurgery. The results were presented at domestic as well as international meetings including Annual Meetings of the Japan Neurosurgical Society and Annual Meetings of American Association of Neurological Surgeons.

Our department has maintained prominent basic research activities as well. The fields of our current research are as follows:

1) Genetic analyses of cerebrovascular diseases and benign brain tumors

We are conducting genetic analysis research for cerebrovascular diseases and benign brain tumors with the aim of identifying molecular markers with high clinical significance and elucidating the pathogenic mechanism.

Specially, genes such as *RNF213* in moyamoya disease, *NF2* in meningioma and schwannoma, *CCM* in cerebral cavernous malformation were analyzed. In addition, comprehensive genetic analyses, including analysis of whole exome sequences, were performed to identify novel disease-related genes..

In the field of cerebrovascular disease, analysis of the *RNF213* gene revealed that *RNF213* variant is associated with not only moyamoya disease but also various intracranial artery stenosis. Furthermore,

genome wide association study of intracranial artery stenosis was performed, and disease related gene polymorphisms were clarified. In addition, we have identified disease-related gene in venous malformations that occur in the head and conducting functional analysis.

In the field of benign brain tumors, we improved the diagnostic rate of somatic mosaics of neurofibromatosis type 2 (NF2) by analyzing DNA from various tissues and reveals the phenotypic characteristics of NF2 somatic mosaics. In the genetic analysis of meningioma, we revealed the association between genetic variants, pathological diagnosis, and anatomical site. We are now conducting research to clarify the characteristic of the changes in gene background during the recurrence of meningiomas.

2) Development of new therapeutic modalities for malignant brain tumors

Genotyping is now widely accepted as an essential component of pathological diagnosis in glioma. We have been routinely analysing surgically resected tumor specimens in a semi-prospective fashion. The genetic analyses include sequencing of *IDH1/2*, *TERT* promoter and histone 3-coding genes, 1p/19q codeletion, 7+/10-, *EGFR* amplification, *CDKN2A* deletion, and methylation analysis of the *MGMT* promoter. These molecular analyses are now indispensable for guiding the best treatment according to the WHO 2021 classification. In addition, we have been searching for novel biomarkers and therapeutic targets using comprehensive genetic and epigenetic analyses with multi-omics analyses, and methylation analysis. The current focus of our genome study is on spinal astrocytoma and ependymoma. Our particular interest also lies in heterogeneity and malignant progression of glioma, especially from immune-oncological perspectives.

To develop a novel strategy for the treatment of glioma, we isolate brain tumor initiating cells, which are supposed to be responsible for resistance to conventional therapies, from surgical specimens, and utilize them in many aspects of our studies.

Furthermore, we are at the frontier in the field of pediatric brain tumor research, especially on CNS germ cell tumors. We have been publishing important articles regarding basic, translational and clinical research.

Multi-omics genomic investigation into the pathogenesis, and clinical trials by Japan Children's Cancer Group, are ongoing.

We have been collaborating with basic research laboratories both within and outside our university. This has led to the development of novel fluorescence probes specifically designed to detect glioma, with the hope that fluorescence-guided surgery may enable a greater extent of resection. Additionally, newer technologies such as single-cell RNA sequencing, spatial transcriptomics, and long-read sequencing, in collaboration with major laboratories, have been implemented in our investigations, broadening the scope of our research.

3) Development and evaluation of function-preserving and less invasive treatment of intractable epilepsy

We have been promoting the research on development, evaluation and standardization of the novel treatment for intractable epilepsy. Particularly, in order to improve the outcome of epilepsy surgery for MRI-negative cases, we are seeking to increase the accuracy of localizing epileptic focus using intracranial electrodes. In addition to the state-of-art technologies such as time-frequency analysis and cortico-cortical evoked potentials, we are developing next-generation intracranial electrodes and accelerating research to identify epileptogenic network. At the same time, we aim to evaluate the effectiveness of function-preserving procedures such as multiple hippocampal transection, which has been originally developed in Japan. Also, as the first facility to introduce vagus nerve stimulation (VNS) therapy in Japan, we are participating in an international collaborative research on the verification of the effectiveness of VNS in the real world.

4) Research on brain function using non-invasive and invasive techniques

We have been studying human brain function using not only non-invasive techniques such as fMRI, MEG, NIRS but also electrocorticography (ECoG) obtained by intracranial electrodes implanted in epilepsy patients. The latter is our markedly advantageous feature that enables us to extract brain information with much higher spatial resolution and SN ratio. We aim to understand brain mechanisms as complicated network systems and to improve the reliability of non-invasive

techniques. Since ECoG is a strong candidate for a decoding source of brain-computer interface (BCI), we are planning to expand the research on this field to clinical implementation of BCI for communication and motor control in cooperation with other brain research laboratories and engineering laboratories.

5) Clinical applications of the functional brain imaging and operative simulation using three-dimensional computer graphics for neurosurgery

Our department intensively utilizes various kinds of functional and metabolic imaging modalities including magnetoencephalography, functional MRI, and diffusion tensor imaging-based tractography for presurgical brain mapping. Combining the results of the multimodalities enables to visualize all cortical and subcortical networks of the motor, language and other cognitive functions in each patient. Furthermore, we succeeded to import the combined information into a neuronavigation system (functional neuronavigation), which quickly and accurately indicates the eloquent brain areas. We could develop virtual reality operative simulation using multi-modal fusion three-dimensional computer graphics. Then, it was possible to precisely examine surgical strategy.

6) Gamma knife radiosurgery

Gamma knife is a kind of devices for stereotactic radiosurgery in which high doses of radiation are delivered at one session and has been widely accepted as one of treatment options for various intracranial disorders such as brain tumors, vascular disorders and functional disorders. The first gamma knife in Japan was introduced at our department and diverse clinical results have been published. Recently, less invasive treatment has taken on an added significance in the field of neurosurgery as well. Therefore, appropriate combination of radical surgery and radiosurgery is necessary to manage difficult-to-treat lesions such as skull base tumors and deeply seated cerebral arteriovenous malformations, and thus gamma knife radiosurgery would play a more important role in neurosurgery. Further, technological progress has refined treatment as an example of integration of diffusion tensor tractography which was firstly attempted at our department. Such technological progresses might contribute to better outcomes of

gamma knife radiosurgery in the future.

References (2023)

1. Dofuku S., Sonehara K., Miyawaki S., Sakaue S., Imai H., Shimizu M., Hongo H., Shinya Y., Ohara K., Teranishi Y., Okano A., Ono H., Nakatomi H., Teraoka A., Yamamoto K., Maeda Y., Nii T., Kishikawa T., Suzuki K., Hirata J., Takahashi M., Matsuda K., Kumanogoh A., Matsuda F., Okada Y., Saito N. Genome-Wide Association Study of Intracranial Artery Stenosis Followed by Phenome-Wide Association Study. **Translational stroke research** 14(3):322-333, 2023 doi: 10.1007/s12975-022-01049-w
2. Hanakita S., Shin M., Hasegawa H., Shojima M., Ohara K., Shinya Y., Kawashima M., Kondo K., Saito N. Endoscopic Extended Transsphenoidal Surgery Aiming for Radical Resection of Skull Base Tumors Involving Cavernous Sinus: Assessment of Resectability and Risks of Complications. **Operative neurosurgery (Hagerstown, Md)** 25(3):260-268, 2023 doi: 10.1227/ons.0000000000000749
3. Hasegawa H., Kiyofuji S., Umekawa M., Shinya Y., Okamoto K., Shono N., Kondo K., Shin M., Saito N. Profiles of central nervous system surgical site infections in endoscopic transnasal surgery exposing the intradural space. **The Journal of hospital infection**, 2023 doi: 10.1016/j.jhin.2023.06.033
4. Hasegawa H., Shin M., Shinya Y., Kashiwabara K., Kikuta S., Kondo K., Saito N. Long-term Outcomes of Non-vascularized Multilayer Fascial Closure Technique for Dural Repair in Endoscopic Transnasal Surgery: Efficacy, Durability, and Limitations. **World Neurosurg** 175:e97-e107, 2023 doi: 10.1016/j.wneu.2023.03.035
5. Hasegawa H., Shinya Y., Ono M., Kikuta S., Kondo K., Saito N. Kashimé: A Novel Knotless Surgical Suture to Simplify Dural Stitches in Endoscopic Transnasal Surgery. **Operative neurosurgery (Hagerstown, Md)** 24(4):417-424, 2023 doi: 10.1227/ons.0000000000000545
6. Hirano Y., Miyawaki S., Imai H., Hongo H., Koizumi S., Yajima H., Torazawa S., Ishigami D., Kiyofuji S., Saito N. Bypass Surgery for Adult-

- Onset Hemorrhagic Moyamoya Disease: Analysis Classified by Site of Initial Bleeding. **World Neurosurg** 178:e585-e594, 2023 doi: 10.1016/j.wneu.2023.07.130
7. Hirano Y., Koizumi S., Shojima M., Ishikawa O., Kiyofuji S., Umekawa M., Saito N. Double-catheter technique for the embolization of recurrent cerebral aneurysms: A single-center experience. **Surg Neurol Int** 14:273, 2023 doi: 10.25259/sni_460_2023
 8. Hirano Y., Miyawaki S., Imai H., Hongo H., Teranishi Y., Ishigami D., Sakai Y., Shimada D., Umekawa M., Segawa M., Koizumi S., Ono H., Nakatomi H., Saito N. Clinical and Genetic Characteristics of Patients with Moyamoya Disease who Experienced Both Ischemic and Hemorrhagic Events. **World Neurosurg** 172:e438-e446, 2023 doi: 10.1016/j.wneu.2023.01.047
 9. Hongo H., Miyawaki S., Teranishi Y., Ishigami D., Ohara K., Sakai Y., Shimada D., Umekawa M., Koizumi S., Ono H., Nakatomi H., Saito N. Genetics of brain arteriovenous malformations and cerebral cavernous malformations. **Journal of human genetics** 68(3):157-167, 2023 doi: 10.1038/s10038-022-01063-8
 10. Hongo H., Miyawaki S., Teranishi Y., Mitsui J., Katoh H., Komura D., Tsubota K., Matsukawa T., Watanabe M., Kurita M., Yoshimura J., Dofuku S., Ohara K., Ishigami D., Okano A., Kato M., Hakuno F., Takahashi A., Kunita A., Ishiura H., Shin M., Nakatomi H., Nagao T., Goto H., Takahashi S. I., Ushiku T., Ishikawa S., Okazaki M., Morishita S., Tsuji S., Saito N. Somatic GJA4 gain-of-function mutation in orbital cavernous venous malformations. **Angiogenesis** 26(1):37-52, 2023 doi: 10.1007/s10456-022-09846-5
 11. Kiyofuji S., Kin T., Saito T., Koike T., Takeda Y., Uchida T., Sato K., Shono N., Niwa R., Furuta Y., Saito N. Invention of an Online Interactive Virtual Neurosurgery Simulator With Audiovisual Capture for Tactile Feedback. **Operative neurosurgery (Hagerstown, Md)** 24(2):194-200, 2023 doi: 10.1227/ons.0000000000000474
 12. Koizumi S., Shojima M., Ota T., Dofuku S., Miyawaki S., Kiyofuji S., Maeda K., Ochi T., Ito A., Hidaka Y., Oya S., Saito A., Yoshikawa G., Yanai K., Inoue T., Tsunoda S., Hoya K., Saito N. Long-Term Stability of Patients Undergoing Endovascular Parent Artery Occlusion of Their Intracranial Artery. **Stroke: Vascular and Interventional Neurology** 3(6):e000968, 2023 doi: doi:10.1161/SVIN.123.000968
 13. Kuroda S., Yamamoto S., Funaki T., Fujimura M., Kataoka H., Hishikawa T., Takahashi J., Endo H., Nariai T., Osato T., Saito N., Sato N., Hori E., Ito Y. M., Miyamoto S. Five-Year Stroke Risk and Its Predictors in Asymptomatic Moyamoya Disease: Asymptomatic Moyamoya Registry (AMORE). **Stroke** 54(6):1494-1504, 2023 doi: 10.1161/strokeaha.122.041932
 14. Kurogi R., Kada A., Ogasawara K., Nishimura K., Kitazono T., Iwama T., Matsumaru Y., Sakai N., Shiokawa Y., Miyachi S., Kuroda S., Shimizu H., Yoshimura S., Osato T., Horie N., Nagata I., Nozaki K., Date I., Hashimoto Y., Hoshino H., Nakase H., Kataoka H., Ohta T., Fukuda H., Tamiya N., Kurogi A. I., Ren N., Nishimura A., Arimura K., Shimogawa T., Yoshimoto K., Onozuka D., Ogata S., Hagihara A., Saito N., Arai H., Miyamoto S., Tominaga T., Iihara K. National trends in the outcomes of subarachnoid haemorrhage and the prognostic influence of stroke centre capability in Japan: retrospective cohort study. **BMJ Open** 13(4):e068642, 2023 doi: 10.1136/bmjopen-2022-068642
 15. Matsushashi A., Tanaka S., Takami H., Nomura M., Ikemura M., Matsubayashi Y., Shinoda Y., Yamada K., Sakai Y., Karasawa Y., Takayanagi S., Saito N. Recurrent glioblastoma metastatic to the lumbar vertebra: A case report and literature review: Surgical oncology. **Frontiers in oncology** 13:1101552, 2023 doi: 10.3389/fonc.2023.1101552
 16. Matsumoto H., Shinya Y., Miyawaki S., Shin M., Koizumi S., Sato D., Hinata M., Ikemura M., Kiyofuji S., Kin T., Iwanaga M., Shimizu M., Nakatomi H., Saito N. White epidermoid cyst transformation after stereotactic radiosurgery: illustrative case. **Journal of neurosurgery Case lessons** 5(24), 2023 doi: 10.3171/case2376
 17. Ogawa S., Miyawaki S., Imai H., Hongo H., Umekawa M., Kiyofuji S., Ishigami D., Sakai Y., Torazawa S., Hirano Y., Koizumi S., Saito N.

- Cerebrovascular Events During Treatment for Systemic Malignant Tumors in Patients with Moyamoya Disease. **World Neurosurg** 179:e314-e320, 2023 doi: 10.1016/j.wneu.2023.08.083
18. Ohara K., Miyawaki S., Nakatomi H., Okano A., Teranishi Y., Shinya Y., Ishigami D., Hongo H., Takayanagi S., Tanaka S., Shinozaki-Ushiku A., Kohsaka S., Kage H., Oda K., Miyagawa K., Aburatani H., Mano H., Tatsuno K., Saito N. Case report and literature review: exploration of molecular therapeutic targets in recurrent malignant meningioma through comprehensive genetic analysis with Todai OncoPanel. **Frontiers in neurology** 14:1270046, 2023 doi: 10.3389/fneur.2023.1270046
 19. Rai Y., Takami H., Kawaguchi K., Takayanagi S., Tanaka S., Yasunaga Y., Saito N. Brain Metastasis Mimicking Glioma on Imaging Appearance During Tyrosine Kinase Inhibitor Administration: A Case Series and Literature Review. **Cureus** 15(8):e43591, 2023 doi: 10.7759/cureus.43591
 20. Rai Y., Umekawa M., Shinya Y., Hasegawa H., Katano A., Kondo K., Shinozaki-Ushiku A., Saito N. Stereotactic radiosurgery for recurrent skull base polymorphous adenocarcinoma invading the cavernous sinus: illustrative case. **Journal of neurosurgery Case lessons** 5(19), 2023 doi: 10.3171/case23103
 21. Sakai Y., Yoshikawa G., Koizumi S., Ishikawa O., Saito A., Sato K. Complete Recanalization in Mechanical Thrombectomy Is Associated with Favorable Functional Outcome for M2 Occlusions. **J Neuroendovasc Ther** 17(1):15-21, 2023 doi: 10.5797/jnet.oa.2022-0057
 22. Sato D., Takami H., Takayanagi S., Taoka K., Tanaka M., Matsuura R., Tanaka S., Saito N. Lymphoproliferative disorder during temozolomide therapy; a representative case of a formidable complication and management challenges. **BMC Neurol** 23(1):224, 2023 doi: 10.1186/s12883-023-03274-8
 23. Sato D., Takami H., Takayanagi S., Ikemura M., Matsuura R., Tanaka S., Saito N. Intraventricular central neurocytoma molecularly defined as extraventricular neurocytoma: a case representing the discrepancy between clinicopathological and molecular classifications. **Brain Tumor Pathol** 40(4):230-234, 2023 doi: 10.1007/s10014-023-00469-2
 24. Sato D., Koizumi S., Umekawa M., Kioyofuji S., Ando M., Ono M., Saito N. Controversies and challenges of coil embolization for intracranial aneurysm in a continuous-flow LVAD implanted patient: A case report. **Surg Neurol Int** 14:34, 2023 doi: 10.25259/sni_1101_2022
 25. Sato D., Hasegawa H., Nishijima H., Kawase K., Okamoto K., Iwasaki A., Shinya Y., Abe M., Miyazaki Y., Saito N. Intracranial aspergilloma mimicking metachronous meningioma following transsphenoidal removal of a tuberculum sellae meningioma: illustrative case. **Journal of neurosurgery Case lessons** 5(5), 2023 doi: 10.3171/case22519
 26. Sato D., Takami H., Tanaka S., Takayanagi S., Ikemura M., Saito N. Long-term survival after corpectomy in a case of spinal cord diffuse midline glioma, H3K27-altered: illustrative case. **Journal of neurosurgery Case lessons** 6(25), 2023 doi: 10.3171/case23296
 27. Shima Y., Sasagawa S., Ota N., Oyama R., Tanaka M., Kubota-Sakashita M., Kawakami H., Kobayashi M., Takubo N., Ozeki A. N., Sun X., Kim Y. J., Kamatani Y., Matsuda K., Maejima K., Fujita M., Noda K., Kamiyama H., Tanikawa R., Nagane M., Shibahara J., Tanaka T., Rikitake Y., Mataga N., Takahashi S., Kosaki K., Okano H., Furihata T., Nakaki R., Akimitsu N., Wada Y., Ohtsuka T., Kurihara H., Kamiguchi H., Okabe S., Nakafuku M., Kato T., Nakagawa H., Saito N., Nakatomi H. Increased PDGFRB and NF- κ B signaling caused by highly prevalent somatic mutations in intracranial aneurysms. **Science translational medicine** 15(700):eabq7721, 2023 doi: 10.1126/scitranslmed.abq7721
 28. Shinya Y., Hasegawa H., Shin M., Kashiwabara K., Kawashima M., Hanakita S., Koga T., Koizumi S., Katano A., Suzuki Y., Saito N. Age-Dependent Hemorrhage Risk and Obliteration Benefit After Radiosurgery for Brain Arteriovenous Malformation. **Int J Radiat Oncol Biol Phys** 116(5):1126-1134, 2023 doi: 10.1016/j.ijrobp.2023.02.059
 29. Shinya Y., Hasegawa H., Shin M., Kawashima M., Koizumi S., Katano A., Suzuki Y., Kashiwabara K.,

- Saito N. In Reply: Stereotactic Radiosurgery Provides Long-Term Safety for Patients With Arteriovenous Malformations in the Diencephalon and Brainstem: The Optimal Dose Selection and Long-Term Outcomes. **Neurosurgery** 92(2):e42-e43, 2023 doi: 10.1227/neu.0000000000002279
30. Shinya Y., Hasegawa H., Kawashima M., Koizumi S., Katano A., Umekawa M., Saito N. Prognosis of Rotational Angiography-Based Stereotactic Radiosurgery for Dural Arteriovenous Fistulas: A Retrospective Analysis. **Neurosurgery** 92(1):167-178, 2023 doi: 10.1227/neu.0000000000002168
 31. Shinya Y., Hasegawa H., Shin M., Kawashima M., Umekawa M., Katano A., Ikemura M., Ushiku T., Ohara K., Okano A., Teranishi Y., Miyawaki S., Saito N. Optimizing Prognostic Predictions and Treatment Strategies in Postoperative World Health Organization Grade 1 Skull Base Meningioma: Potential Role of Ki-67 Labeling Index in Stereotactic Radiosurgery. **World Neurosurg** 178:266-267, 2023 doi: 10.1016/j.wneu.2023.07.072
 32. Shinya Y., Hasegawa H., Shin M., Kawashima M., Umekawa M., Katano A., Ikemura M., Ushiku T., Ohara K., Okano A., Teranishi Y., Miyawaki S., Saito N. Long-Term Outcomes of Stereotactic Radiosurgery for Postoperative World Health Organization Grade I Skull Base Meningioma: Utility of Ki-67 Labeling Index as a Prognostic Indicator. **Neurosurgery** 93(5):1144-1153, 2023 doi: 10.1227/neu.0000000000002546
 33. Takami H., Graffeo C. S., Perry A., Giannini C., Nakazato Y., Saito N., Matsutani M., Nishikawa R., Daniels D. J., Ichimura K. Impact of tumor markers on diagnosis, treatment and prognosis in CNS germ cell tumors: correlations with clinical practice and histopathology. **Brain Tumor Pathol** 40(2):124-132, 2023 doi: 10.1007/s10014-023-00460-x
 34. Takami H., Mukasa A., Takayanagi S., Koike T., Matsuura R., Ikemura M., Ushiku T., Yoshikawa G., Shibahara J., Tanaka S., Saito N. Correction: Morphologically, genetically and spatially mixed astrocytoma and oligodendroglioma; chronological acquisition of 1p/19q codeletion and CDKN2A deletion: a case report. **Brain Tumor Pathol** 40(2):142, 2023 doi: 10.1007/s10014-023-00449-6
 35. Takami H., Mukasa A., Takayanagi S., Koike T., Matsuura R., Ikemura M., Ushiku T., Yoshikawa G., Shibahara J., Tanaka S., Saito N. Morphologically, genetically and spatially mixed astrocytoma and oligodendroglioma; chronological acquisition of 1p/19q codeletion and CDKN2A deletion: a case report. **Brain Tumor Pathol** 40(1):26-34, 2023 doi: 10.1007/s10014-022-00448-z
 36. Takami H., Tanaka S., Takayanagi S., Nakatomi H., Saito N. Indocyanine green illuminates the way to cut the tentorium in occipital transtentorial approach: technical note. **Br J Neurosurg** 37(6):1925-1927, 2023 doi: 10.1080/02688697.2021.1927982
 37. Takami H., Satomi K., Fukuoka K., Nakamura T., Tanaka S., Mukasa A., Saito N., Suzuki T., Yanagisawa T., Sugiyama K., Kanamori M., Kumabe T., Tominaga T., Tamura K., Maehara T., Nonaka M., Asai A., Yokogami K., Takeshima H., Iuchi T., Kobayashi K., Yoshimoto K., Sakai K., Nakazato Y., Matsutani M., Nagane M., Nishikawa R., Ichimura K. Distinct patterns of copy number alterations may predict poor outcome in central nervous system germ cell tumors. **Sci Rep** 13(1):15760, 2023 doi: 10.1038/s41598-023-42842-3
 38. Teranishi Y., Miyawaki S., Nakatochi M., Okano A., Ohara K., Hongo H., Ishigami D., Sakai Y., Shimada D., Takayanagi S., Ikemura M., Komura D., Katoh H., Mitsui J., Morishita S., Ushiku T., Ishikawa S., Nakatomi H., Saito N. Meningiomas in patients with neurofibromatosis type 2 predominantly comprise 'immunogenic subtype' tumours characterised by macrophage infiltration. **Acta neuropathologica communications** 11(1):156, 2023 doi: 10.1186/s40478-023-01645-3
 39. Tsunoda S., Inoue T., Ohwaki K., Takeuchi N., Shinkai T., Fukuda A., Segawa M., Kawashima M., Akabane A., Miyawaki S., Saito N. Association Between Frontal Lobe Hemodynamics and Neurocognitive Dysfunction in Adults With Moyamoya Disease: Retrospective Cohort Analysis. **Neurosurgery** 92(3):547-556, 2023 doi: 10.1227/neu.0000000000002246
 40. Uchida T., Kin T., Saito T., Shono N., Kiyofuji S.,

nmc.2022-0301

- Koike T., Sato K., Niwa R., Takashima I., Oyama H., Saito N. De-Identification Technique with Facial Deformation in Head CT Images. **Neuroinformatics** 21(3):575-587, 2023 doi: 10.1007/s12021-023-09631-9
41. Uchida T., Kin T., Sato K., Koike T., Kiyofuji S., Takeda Y., Niwa R., Saito T., Takashima I., Kawahara T., Miyawaki S., Oyama H., Saito N. Reproducibility of Facial Information in Three-Dimensional Reconstructed Head Images: An Exploratory Study. **Current medical imaging** 19(12):1387-1393, 2023 doi: 10.2174/1573405619666230123105057
 42. Uchikawa H., Kin T., Koizumi S., Sato K., Uchida T., Takeda Y., Koike T., Kiyofuji S., Yamashiro S., Mukasa A., Saito N. Aneurysmal Inflow Rate Coefficient Predicts Ultra-early Rebleeding in Ruptured Intracranial Aneurysms: Preliminary Report of a Computational Fluid Dynamics Study. **Neurol Med Chir (Tokyo)** 63(10):450-456, 2023 doi: 10.2176/jns-nmc.2023-0003
 43. Umekawa M., Saito K., Shinya Y., Hasegawa H., Kawashima M., Teranishi Y., Katano A., Ikemura M., Saito N. Stereotactic radiosurgery for recurrent pleomorphic adenoma of the lacrimal gland: a case report. **Acta Neurochir (Wien)** 165(1):221-224, 2023 doi: 10.1007/s00701-022-05384-7
 44. Umekawa M., Shinya Y., Hasegawa H., Katano A., Saito N. Primary Stereotactic Radiosurgery Provides Favorable Tumor Control for Intraventricular Meningioma: A Retrospective Analysis. **Journal of clinical medicine** 12(3), 2023 doi: 10.3390/jcm12031068
 45. Yajima H., Miyawaki S., Sayama S., Kumasawa K., Ikemura M., Imai H., Hongo H., Hirano Y., Ishigami D., Torazawa S., Kiyofuji S., Koizumi S., Saito N. Hypertensive disorders of pregnancy in moyamoya disease: A single institution experience. **J Stroke Cerebrovasc Dis** 32(11):107377, 2023 doi: 10.1016/j.jstrokecerebrovasdis.2023.107377
 46. Yajima H., Koizumi S., Kanda T., Shono N., Kin T., Saito N. Possible Association between Recurrent Chronic Subdural Hematoma and Dural Arteriovenous Fistula: A Case Report with Three-dimensional Fusion Images. **NMC case report journal** 10:41-45, 2023 doi: 10.2176/jns-

Social Medicine

1. Occupational, Environmental and Preventive Medicine

Department of Molecular Preventive Medicine

Professor

Shumpei Ishikawa, M.D., Ph.D.

Associate Professor

Hiroto Katoh, M.D., Ph.D.

Assistant Professor

Daisuke Komura, M.D., Ph.D.

Miwako Kakiuchi, M.D., Ph.D.

Homepage <https://plaza.umin.ac.jp/prm/>

Introduction and Organization

Department of Preventive Medicine is the oldest laboratory in the University of Tokyo, established by Masanori Ogata in 1885. Ever since, for more than 130 years, the laboratory has been a hub to important research leading to disease prevention and developed and produced core human resources in public health administration. The philosophy of the Department to Preventive Medicine has not changed throughout its history, but its focus of research has changed from time to time, like infectious diseases and occupational health to name a few, to meet the expectations of the society. Eventually, in response to the completion of the Human Genome Project and the recent advancement in molecular biology, the laboratory had changed its name to the Department of Molecular Preventive Medicine. Under Professor Koji Matsushima, the 8th director of the laboratory, research was actively conducted to clarify inflammation/immune phenomenon with focus on cytokines in disease background, and its clinical application for secondary/tertiary prevention. In December 2018, Professor Shumpei Ishikawa became the 9th director, and in April 2019, he changed the name of the department back to Preventive Medicine.

Currently, our lab includes (besides the professor, the associate professor, and the assistant professors) 10

students (3 are from outside of the University of Tokyo), 1 academic professional staff, 1 technical staff, 2 technical assistants, 4 visiting researchers, 2 project specialist.

Teaching activities

We give “Preventive Medicine” lecture course to third-year undergraduate students in the school of medicine, practical courses to fifth-year undergraduate students, “Introduction to Preventive Medicine” in medical science master’s program, and “Surviving Cancer in Asia,” a doctoral program common course in medicine.

In the “Preventive Medicine” lecture course, specific emphases are on alteration of the disease pattern associated with social change, basic concepts of occupational and mental health, and information science as a key to the understanding of genome and abundant bio/health data, which is a basis of disease predisposition.

In the practical course for fifth-year undergraduate students, three staff members are in charge of environmental microbiology measurement, cancer genome data analysis, and medical image analysis. In the environmental microbiological measurement, students collect samples from various environments

and analyze the distribution of microorganisms in the samples using a long-read sequencer. In cancer genome data analysis, students use publicly available single-cell transcriptome data and analyze them from their own unique perspectives to make sense of the cancer microenvironment, etc. In medical image analysis, students classify histopathological images using deep learning and analyze and discuss the impact of various techniques to improve its accuracy.

Research activities

In Department of Preventive Medicine, we conduct research based on genome science and information science to explore the appropriate points of intervention for various health issues, in particular, cancer prevention and treatment. Cancer and inflammation/immune diseases are complex systems comprised of numerous types of cells. We aim to elucidate the dynamics of such complex systems by collecting extensive data at genome-level, as well as to explore specific phenomena which may serve as intervenable preventive/therapeutic targets, and to evaluate their significance in the related diseases. In addition, we are developing bioinformatics technology to extract essential information from massive and multi-dimensional biological data, e.g., genome sequence and images, for human interpretation by techniques such as dimensionality reduction and visualization.

Our current primary focus areas of research are as follow:

1. Immune Repertoire Analysis to Reveal Internal/External Immune Environment Profiles in Individuals

Antigen receptor genes of human lymphocyte undergo somatic hypermutation to acquire extensive diversity. The entire set of antigen receptors in lymphocyte population is called immune repertoire, and its profiling in individuals has now become possible thanks to the advancement in genome analysis technology such as next-generation sequencing (NGS). Immune repertoires are considered to reflect immune history affected by external factors, e.g., pathogens and foods that the individual has encountered, and by internal factors, e.g., self-antigens and cancer antigens.

In the department of Preventive Medicine, we are trying to develop a method to extract not only current disease conditions but also other relevant health information, such as past disease history and lifestyles, by analyzing immune repertoires. In particular, in immune repertoire analysis using gastric cancer and gastric mucosa tissues, we combine the results with cancer genome and microbiome analyses to decipher immune history with regard to cancer antigens and *H. pylori* in its entirety, and revealed that the sulfated glycosaminoglycans are major and functional B cell antigens in human cancers. We also use information analysis technique such as deep learning to analyze information related to cancer prevention and treatment. We are also synthesizing antibodies from this immune repertoire data to develop antibody drugs against cancer.

2. Cancer Genome Analysis to Explore Carcinogenic Factors and Point of Intervention

We are combining human clinical cancer tissues with NGS to achieve a comprehensive understanding of the cancer genome. Whole cancer genome sequencing will provide numerous information, such as the driver genes, which would serve direct therapeutic targets, and the genetic background of an individual related to carcinogenic predispositions. It also enables mutation signature analysis to reveal environmental factors which are also possible carcinogenic predispositions. The obtained information is processed as a whole by the combination of bioinformatics and experimental validation to explore the appropriate points of intervention for cancer prevention and treatment, which are crucial for health in our country. We have identified RHOA driver mutation in diffuse-type gastric adenocarcinoma by cancer genome sequencing. In addition, we performed trans-ethnic genome analysis of gastric cancer and showed the existence of East Asian-specific gastric cancer induced by alcohol drinking and smoking. Currently, we are regarding cancer tissues as a whole using clinical cancer tissues and patient-derived xenografts (PDX), by applying genomics point of view, i.e., single-cell analysis, to cancer cells, immune cells, and vascular stroma cells that comprise cancer tissue, to elucidate carcinogenic and progression factors and points of intervention from higher dimensions.

We also conducted large-scale single-cell RNA sequencing and spatial gene expression analysis of gastric mucosa, revealing gene expression profiles including spatial information of cells constituting the stomach. Through this analysis, we identified LEFTY1 as a novel stem cell marker for epithelial cells and discovered a subpopulation of fibroblasts that increases prior to intestinal metaplasia. These findings are expected to provide new insights into understanding the homeostatic maintenance mechanisms of gastric mucosa and studying gastric cancer development mechanisms.

3. Contribution to Elimination of Medical Care Disparities by Histopathological Image Analysis

In the modern era where biomedical information is growing rapidly, extracting essential information from enormous amounts of biological data through dimension compression is extremely important.

In the Department of Preventive Medicine, we have developed technology using deep neural networks to extract essential cancer characteristics from histopathological images (deep texture) and are working on developing tools to achieve uniform pathological diagnoses and eliminate regional healthcare disparities. As part of this initiative, we have developed Luigi, a content-based image retrieval system for cancer histopathological images, which is available as a website (<https://luigi-pathology.com/>) and smartphone application. The Luigi database contains histopathological images and their deep texture features from more than 7,000 cases across 32 cancer types from The Cancer Genome Atlas. Users can find similar cases by uploading histopathological images to the system. We are currently expanding our case database in collaboration with various medical institutions. Furthermore, through integrated analysis of histopathological information and cancer genomic information using deep texture analysis, we are also developing a system that enables seamless connection between routine laboratory tests performed in small and medium-sized medical facilities and cancer genomic medicine provided at core hospitals.

From 2023, as part of action plan for whole genome analysis, we began collecting pathological images of whole genome analysis cases. Centered around the

Department of Preventive Medicine, we are advancing the collection of pathological images and pathology reports from various medical facilities, while simultaneously preparing for the development of a foundation model for pathological images utilizing these data.

Publications

1. Akiyama, Y., Harada, K., Miyakawa, J., Kreder, K. J., O'Donnell, M. A., Daichi, M., Katoh, H., Hori, M., Owari, K., Futami, K., Ishikawa, S., Ushiku, T., Kume, H., Homma, Y., & Luo, Y. (2023). Th1/17 polarization and potential treatment by an anti-interferon- γ DNA aptamer in Hunner-type interstitial cystitis. **iScience**, 108262. <https://doi.org/10.1016/j.isci.2023.108262>
2. Akiyama, Y., Sonehara, K., Maeda, D., Katoh, H., Naito, T., Yamamoto, K., Biobank Japan Project, Morisaki, T., Ishikawa, S., Ushiku, T., Kume, H., Homma, Y., & Okada, Y. (2023). Genome-wide association study identifies risk loci within the major histocompatibility complex region for Hunner-type interstitial cystitis. **Cell Reports. Medicine**, 4(7), 101114. <https://doi.org/10.1016/j.xcrm.2023.101114>
3. Herdiantoputri, R. R., Komura, D., Fujisaka, K., Ikeda, T., & Ishikawa, S. (2023). Deep texture representation analysis for histopathological images. **STAR Protocols**, 4(2), 102161. <https://doi.org/10.1016/j.xpro.2023.102161>
4. Herdiantoputri, R. R., Komura, D., Ikeda, T., & Ishikawa, S. (2023). Head and Neck Tumor Histopathological Image Representation with Pre-Trained Convolutional Neural Network and Vision Transformer. **Journal of Dentistry Indonesia**, 30(1), 41–47. <https://doi.org/10.14693/jdi.v30i1.1501>
5. Katoh, H., Komura, D., Furuya, G., & Ishikawa, S. (2023). Immune repertoire profiling for disease pathobiology. **Pathology International**, 73(1), 1–11. <https://doi.org/10.1111/pin.13284>
6. Kojima, M., Yokota, M., Yanagisawa, N., Kitamura, S., Amemiya, K., Kawano, S., Tsukada, Y., Sakuyama, N., Nagayasu, K., Hashimoto, T., Nakashima, K., Jiang, K., Kanemitsu, Y., Fujita, F., Akiba, J., Notohara, K., Itakura, J., Sekine, S.,

- Sakashita, S., ... Ochiai, A. (2023). Assessment of Elastic Laminal Invasion Contributes to an Objective pT3 Subclassification in Colon Cancer. **The American Journal of Surgical Pathology**. <https://doi.org/10.1097/PAS.0000000000002090>
7. Komura, D., Onoyama, T., Shinbo, K., Odaka, H., Hayakawa, M., Ochi, M., Herdiantoputri, R. R., Endo, H., Katoh, H., Ikeda, T., Ushiku, T., & Ishikawa, S. (2023). Restaining-based annotation for cancer histology segmentation to overcome annotation-related limitations among pathologists. **Patterns**, 4(2), 100688. <https://doi.org/10.1016/j.patter.2023.100688>
 8. Matsuno, A., Sumida, H., Nakanishi, H., Ikeyama, Y., Ishii, T., Omori, I., Saito, H., Iwasawa, O., Sugimori, A., Yoshizaki, A., Katoh, H., Ishikawa, S., & Sato, S. (2023). Keratinocyte proline - rich protein modulates immune and epidermal response in imiquimod - induced psoriatic skin inflammation. **Experimental Dermatology**, exd.14960. <https://doi.org/10.1111/exd.14960>
 9. Morisue, R., Kojima, M., Suzuki, T., Watanabe, R., Sakamoto, N., Sakashita, S., Harada, K., Nakai, T., Ishii, G., Nakatsura, T., Gotohda, N., & Ishikawa, S. (2023). Common clinicopathological and immunological features of sarcomatoid carcinoma across organs: A histomorphology-based cross-organ study. **International Journal of Cancer**. <https://doi.org/10.1002/ijc.34680>
 10. Sakata, J., Tatsumi, T., Sugiyama, A., Shimizu, A., Inagaki, Y., Katoh, H., Yamashita, T., Takahashi, K., Aki, S., Kaneko, Y., Kawamura, T., Miura, M., Ishii, M., Osawa, T., Tanaka, T., Ishikawa, S., Tsukagoshi, M., Chansler, M., Kodamad, T., ... Yamatsugu, K. (2023). Antibody-mimetic drug conjugate with efficient internalization activity using anti-Her2 VHH and duocarmycin. **Protein Expression and Purification**, 106375. <https://doi.org/10.1016/j.pep.2023.106375>
 11. Teranishi, Y., Miyawaki, S., Nakatochi, M., Okano, A., Ohara, K., Hongo, H., Ishigami, D., Sakai, Y., Shimada, D., Takayanagi, S., Ikemura, M., Komura, D., Katoh, H., Mitsui, J., Morishita, S., Ushiku, T., Ishikawa, S., Nakatomi, H., & Saito, N. (2023). Meningiomas in patients with neurofibromatosis type 2 predominantly comprise “immunogenic subtype” tumours characterised by macrophage infiltration. **Acta Neuropathologica Communications**, 11(1), 156. <https://doi.org/10.1186/s40478-023-01645-3>
 12. Torazawa, S., Miyawaki, S., Imai, H., Hongo, H., Ishigami, D., Shimizu, M., Ono, H., Shinya, Y., Sato, D., Sakai, Y., Umekawa, M., Kiyofuji, S., Shimada, D., Koizumi, S., Komura, D., Katoh, H., Ishikawa, S., Nakatomi, H., Teraoka, A., & Saito, N. (2023). RNF213 p.Arg4810Lys Wild Type is Associated with De Novo Hemorrhage in Asymptomatic Hemispheres with Moyamoya Disease. **Translational Stroke Research**. <https://doi.org/10.1007/s12975-023-01159-z>
 13. Totoki, Y., Saito-Adachi, M., Shiraishi, Y., Komura, D., Nakamura, H., Suzuki, A., Tatsuno, K., Rokutan, H., Hama, N., Yamamoto, S., Ono, H., Arai, Y., Hosoda, F., Katoh, H., Chiba, K., Iida, N., Nagae, G., Ueda, H., Shihang, C., ... Shibata, T. (2023). Multiancestry genomic and transcriptomic analysis of gastric cancer. **Nature Genetics**, 1–14. <https://doi.org/10.1038/s41588-023-01333-x>
 14. Tsubosaka, A., Komura, D., Kakiuchi, M., Katoh, H., Onoyama, T., Yamamoto, A., Abe, H., Seto, Y., Ushiku, T., & Ishikawa, S. (2023). Stomach encyclopedia: Combined single-cell and spatial transcriptomics reveal cell diversity and homeostatic regulation of human stomach. **Cell Reports**, 42(10), 113236. <https://doi.org/10.1016/j.celrep.2023.113236>
 15. Yukawa, N., Yamada, T., Aoyama, T., Woo, T., Ueda, K., Mastuda, A., Hara, K., Kazama, K., Tamagawa, H., Sato, T., Oshima, T., Suzuki, A., Aburatani, H., Ishikawa, S., Saito, A., Masuda, M., Yoshida, H., & Rino, Y. (2023). Tumor DNA in Peritoneal Lavage as a Novel Biomarker for Predicting Peritoneal Recurrence in Patients With Gastric Cancer. **Anticancer Research**, 43(5), 2069–2076. <https://doi.org/10.21873/anticancer.16367>

Department of Public Health/ Department of Health Policy

Professor

Takahiro Higashi, M.D., Ph.D.

(From September 1, 2022)

Associate Professor

Haruhiko Inada, M.D., Ph.D., M.P.H.

(From February 1, 2023)

Lecturer

Misa Takegami

(from April 1, 2023)

Assistant Professor

Atsushi Miyawaki

(until June 30, 2023)

Ryoko Rikitake

(from July 1, 2023)

Homepage <https://publichealth.m.u-tokyo.ac.jp/>

Introduction and Organization

Modern concepts of public health originated in the Industrial Revolution era in the UK, and since then developed in Western countries. In Japan, these concepts became important and popular in the 1880s, when the Japan Non-governmental Association for Hygiene (a synonym of public health in that age) was established to fight against repeated outbreaks of cholera in Japan.

Public health departments in medical schools in Japan were introduced after the World War II, following the model of the U.S. systems for public health and medical education. The Department of Public Health was established in 1947, in Faculty of Medicine, the University of Tokyo. In 1995, the Department became a part of Division of Social Medicine, Graduate School of Medicine, as the result of the shift to a

graduate school system in the University of Tokyo. In 2007, School of Public Health was established in the University of Tokyo, and the Department became a part of School of Public Health (Department of Health Policy) and remained being a part of Division of Social Medicine (Department of Public Health).

The objectives of the Department are both education and research of public health. The Department trains graduate and undergraduate students through lectures, seminars, field practice, and laboratory work in public health and occupational medicine, for the degrees of Medical Doctor (MD), Master of Public Health (MPH), and Doctor of Medical Sciences (equivalent to PhD). The Department has conducted research on a wide variety for public health issues, including health policy and economics, occupational medicine, clinical epidemiology, health services research, and so on. In

addition, the staff members of the Department have offered public and occupational health services to the governments, industries, and local communities.

In the academic year of 2020, the Department consists of 4 faculty members above listed, 1 project researchers (part-time), 3 supporting staff members, 3 graduate students (2 in PhD program, 1 in professional degree course), and 16 part-time lecturers.

Teaching activities

1) Undergraduate Program (Medical School)

Public health education in the medical program is provided to M2 (4th year), M3 (5th year), and M4 (6th year) students. During the autumn semester of M2, a total of 18 lectures are conducted in the public health systematic course, aiming to provide a comprehensive understanding of the field and basic methodologies. Lecture topics include an introduction to public health, epidemiology, recent developments in Japan's cancer control measures, mental health epidemiology, an introduction to participatory research, social determinants of health, public health administration, health policy, health economics, human ecology, tuberculosis control, maternal and child health, an introduction to space medicine, epidemiology of climate change and planetary health, community healthcare and welfare, and diabetes health policy. Particularly for public health administration, active medical officers from the Ministry of Health, Labour, and Welfare are invited to deliver lectures.

Practical training for M3 students is conducted in collaboration with Department of Preventive Medicine and other departments during one-week sessions in July and September. Students are divided into small groups (32 groups in total) for this training. In the autumn of M4, the department oversees six intensive lectures in social medicine. Topics include public health, healthcare and long-term care, health services research, experiences in responding to COVID-19 at regional public health centers, health policy lectures by active medical officers, perspectives from cancer patients provided by patient advocacy groups, and health economics.

Additionally, the department supports clinical researcher training programs by accepting medical students as part of the initiative.

2) MPH Program

Public Health Preparedness, Health Policy, and Health Administration & Public Health Preparedness Exercise (at Yokohama City Public Health Center).

For Health and Medical Policy Studies, lectures were delivered from various perspectives and positions on healthcare policy.

In Health Crisis Management, lectures covered topics such as disaster medicine, infectious diseases, and radiation crisis management.

3) PhD Program

The Department offers special lectures, seminars, field practice, and laboratory work on public health and occupational medicine to graduate students. In these training, special emphasis has been placed on the following points: (1) how to conduct epidemiological studies, (2) how to use epidemiological and statistical methods, (3) how to use economic concepts and methods in the health fields, (4) how to establish the collaboration with health professionals in the various fields, and (5) how to read and write original papers.

(4) Global Education for Innovation and Leadership (GEfIL):

Lectures (10 sessions) and practical training (11 days) on global health were offered for selected undergraduate students from the 2nd to 4th years across all faculties.

Research activities

Our primary focus is on empirical analyses related to healthcare policy, health policy, and health management.

The main research themes are as follows:

- (1) Research on understanding medical realities to support the promotion of cancer control measures (in collaboration with National Cancer Center in Japan)
- (2) Research to advance measures for rare cancers
- (3) Development of databases to support regional cancer control and specialized cancer fields
- (4) Research on the usefulness of generative AI in cancer consultation support
- (5) Development of a cardiovascular disease database (in collaboration with National Cerebral and

Cardiovascular Center)

(6) Establishing a framework for providing scientific evidence to address challenges in health and medical policy

(7) Research on ensuring safe transportation options for the elderly (in collaboration with University of Tsukuba and others)

(8) Research on the relationship between chronic diseases, medications, and traffic accidents (in collaboration with Nagasaki University, University of Tsukuba, and others)

(9) Research on traffic safety for school routes (in collaboration with the University of Tsukuba and others)

(10) Research on traffic safety in low- and middle-income countries (in collaboration with Johns Hopkins University and others)

(11) Research on fire prevention (in collaboration with University of Tsukuba)

(12) Empirical analysis of the efficiency, equity, and health outcomes of medical care based on incentive structures under Japan's health insurance system

(13) Estimation of disease frequencies and evaluation of healthcare quality using data from receipts, cancer registries, and medical records

(14) Research on the future supply and demand of healthcare workers in Japan, the geographic and specialty distribution of physicians, and residents' access to healthcare

(15) Health services research for the elderly

(16) Physician-related factors affecting health outcomes

(17) Overutilization of healthcare services

References

(Original Article)

- Okuyama A, Kosaka H, Kaibori M, Higashi T, Ogawa A. Activities of daily living after surgery among older patients with gastrointestinal and hepatobiliary-pancreatic cancers: a retrospective observational study using nationwide health services utilisation data from Japan *BMJ Open*. 2023 May 25;13(5):e070415. doi: 10.1136/bmjopen-2022-070415.
- Ogata D, Namikawa K, Nakano E, Fujimori M, Uchitomi Y, Higashi T, Yamazaki N, Kawai A. Epidemiology of skin cancer based on Japan's National Cancer Registry 2016–2017 *Cancer Sci*. 2023 Jul;114(7):2986-2992. doi: 10.1111/cas.15823. Epub 2023 Apr 24.
- Inada H, Tomio J, Nakahara S, Ichikawa M. Association between mandatory cognitive testing for license renewal and motor vehicle collisions and road injuries. *J Am Geriatr Soc*. 2023 Apr; 71(4):1145-1155. doi: 10.1111/jgs.18157. Epub 2023 Jan 25.
- Miyawaki, A., Jena, AB., Burke, LG., Figueroa, JF., & Tsugawa, Y. Association between emergency physicians' age and mortality of medicare patients aged 65 to 89 years after emergency department Visit. *Ann Emerg Med*. 2023 Sep; 82(3):301-312. doi: 10.1016/j.annemergmed.2023.02.010. Epub 2023 Mar 23. (corresponding author)
- Miyawaki, A., Jena, A., Gross, N. & Tsugawa, Y. Comparison of Hospital Outcomes for Medicare Patients Treated by Allopathic versus Osteopathic Hospitalists: An Observational Study. *Ann Intern Med*. 2023 Jun;176(6):798-806. doi: 10.7326/M22-3723. Epub 2023 May 30. (*corresponding author)
- Ishii T, Watanabe T, Higashi T. Differences in the performance of adjuvant chemotherapy between hemodialysis and non-hemodialysis patients. *Cancer Med*. 2023 Feb;12(4):4033-4041. doi: 10.1002/cam4.5258. Epub 2022 Sep 21.
- Abe, K., Kawachi, I., Iba, A., & Miyawaki, A. (2023) In-hospital deaths from ambulatory care-sensitive conditions before and during the COVID-19 pandemic in Japan. *JAMA Netw Open*. 2023 Jun 1;6(6):e2319583. doi: 10.1001/jamanetworkopen.2023.19583..
- Watanabe T, Rikitake R, Kakuwa T, Ichinose Y, Nino M, Mizushima Y, Ota M, Fujishita M, Tsukada Y, Higashi T. Time to treatment initiation for six cancer types: An analysis of data from a nationwide registry in Japan. *World J Surg*. 2023 Apr;47(4):877-886. doi: 10.1007/s00268-022-06883-5. Epub 2023 Jan 6.
- Kusano K, Yamane T, Inoue K, Takegami M, Nakai M, Kanaoka K, Tonegawa-Kuji R, Miyamoto K, Iwasaki YK, Takatsuki S, Nakamura K, Iwanaga Y, Shimizu W. The Japanese Catheter Ablation Registry (J-AB):

- Annual report in 2021. *J Arrhythm*. 2023 Sep 25;39(6):853-859. doi: 10.1002/joa3.12931. eCollection 2023 Dec.
10. Arai R, Okumura Y, Murata N, Fukamachi D, Honda S, Nishihira K, Kojima S, Takegami M, Asaumi Y, Yamashita J, Saji M, Hibi K, Takahashi J, Sakata Y, Takayama M, Sumiyoshi T, Ogawa H, Kimura K, Yasuda S. Prevalence and Impact of Polyvascular Disease in Patients With Acute Myocardial Infarction in the Contemporary Era of Percutaneous Coronary Intervention - Insights From the Japan Acute Myocardial Infarction Registry (JAMIR). *Circ J*. 2024 May 24;88(6):911-920. doi: 10.1253/circj.CJ-23-0477. Epub 2023 Nov 23.
 11. Nishihira K, Honda S, Takegami M, Kojima S, Takahashi J, Itoh T, Watanabe T, Yamashita J, Saji M, Tsujita K, Takayama M, Sumiyoshi T, Kimura K, Yasuda S. Percutaneous coronary intervention for ST-elevation myocardial infarction complicated by cardiogenic shock in a super-aging society. *Eur Heart J Acute Cardiovasc Care*. 2023 Dec 21;12(12):847-855. doi: 10.1093/ehjacc/zuad113.
 12. Morris K, Takegami M, Teramoto K, Murata S, Nakatsuka K, Ogata S, Nishimura K. Cognitive transitions based on functional status in older adults with heart failure: a population-based study. *ESC Heart Fail*. 2023 Dec;10(6):3454-3462. doi: 10.1002/ehf2.14512. Epub 2023 Sep 14.
 13. Suto M, Sugiyama T, Imai K, Furuno T, Hosozawa M, Ichinose Y, Ihana-Sugiyama N, Kodama T, Koizumi R, Shimizu-Motohashi Y, Murata S, Nakamura Y, Niino M, Sato M, Taguchi R, Takegami M, Tanaka M, Tsutsumimoto K, Usuda K, Takehara K, Iso H. Studies of Health Insurance Claims Data in Japan: A Scoping Review. *JMA J*. 2023 Jul 14;6(3):233-245. doi: 10.31662/jmaj.2022-0184. Epub 2023 Jun 19.
 14. Asase M, Watanabe T, Takegami M, Nishimura K, Nin K, Fukushima N. Impact of Different Therapeutic Strategies With Left Ventricular Assist Devices on Health-Related Quality of Life During Prolonged Device-Based Support. *Circ Rep*. 2023 Jun 9;5(7): 289-297. doi: 10.1253/circrep.CR-22-0126. eCollection 2023 Jul 10.
 15. Tomura N, Honda S, Takegami M, Nishihira K, Kojima S, Takayama M, Yasuda S. Characteristics and In-Hospital Outcomes of Patients Who Underwent Coronary Artery Bypass Grafting during Hospitalization for ST-Segment Elevation or Non-ST-Segment Elevation Myocardial Infarction. *Ann Thorac Cardiovasc Surg*. 2024 Jan 25;30(1): 23-00016. doi: 10.5761/atcs.0a.23-00016. Epub 2023 Jul 7.
 16. Tanaka H, Takegami M, Miyake M, Amano M, Kitai T, Fujita T, Koyama T, Ando K, Komiya T, Izumo M, Kawai H, Eishi K, Yoshida K, Kimura T, Nawada R, Sakamoto T, Shibata Y, Fukui T, Minatoya K, Tsujita K, Sakata Y, Kimura T, Nishimura K, Furukawa Y, Izumi C. Association of Left Atrial Size With Stroke or Systemic Embolism in Patients With Atrial Fibrillation Having Undergone Bioprosthetic Valve Replacement From the BPV-AF Registry. *Circ Rep*. 2023; 5:210-216.
 17. Kiyoshige E, Ogata S, O'Flaherty M, Capewell S, Takegami M, Iihara K, Kypridemos C, Nishimura K. Projections of future coronary heart disease and stroke mortality in Japan until 2040: a Bayesian age-period-cohort analysis. *Lancet Reg Health West Pac*. 2022 Nov 15;31:100637. doi: 10.1016/j.lanwpc. 2022.100637. eCollection 2023 Feb..
 18. Ikeda S, Saito S, Hosoki S, Tonomura S, Yamamoto Y, Ikenouchi H, Ishiyama H, Tanaka T, Hattori Y, Friedland RP, Carare RO, Kuriyama N, Yakushiji Y, Hara H, Koga M, Toyoda K, Nomura R, Takegami M, Nakano K, Ihara M. Harboring Cnm-expressing *Streptococcus* mutans in the oral cavity relates to both deep and lobar cerebral microbleeds. *Eur J Neurol*. 2023 Nov;30(11):3487-3496. doi: 10.1111/ene.15720. Epub 2023 Feb 16.
 19. Miyamoto K, Murata S, Takegami M, Nakajima K, Kamakura T, Wada M, Ishibashi K, Inoue Y, Nagase S, Aiba T, Nishimura K, Kusano K. Real-world comparison of in-hospital complications after catheter ablation for atrial fibrillation between non-antivitamin K anticoagulants and warfarin: A propensity-matched analysis using nation-wide database. *Int J Cardiol Heart Vasc*.

- 2023 Jan 11:44:101174. doi: 10.1016/ j.ijcha. 2023.101174. eCollection 2023 Feb.
20. Fukui K, Takahashi J, Hao K, Honda S, Nishihira K, Kojima S, Takegami M, Sakata Y, Itoh T, Watanabe T, Takayama M, Sumiyoshi T, Kimura K, Yasuda S. Disparity of Performance Measure by Door-to-Balloon Time Between a Rural and Urban Area for Management of Patients With ST-Segment Elevation Myocardial Infarction - Insights From the Nationwide Japan Acute Myocardial Infarction Registry. *Circ J*. 2023 Apr 25; 87(5):648-656. doi: 10.1253/circj.CJ-22-0454. Epub 2022 Dec 2.
 21. Rikitake R, Mizushima Y, Yoshimoto S, Higashi T, Satake T, Morizane C, Kawai A. Current status of head and neck sarcomas in Japan in 2016-2019: an analysis using the national cancer registry : *Int J Clin Oncol*. 2024 May;29(5):564-570. doi: 10.1007/ s10147-024-02484-5. Epub 2024 Feb 27.
 22. Wada S, Watanabe T, Ishii T, Ichinose Y, Rikitake R, Ogata D, Nakano E, Namikawa K, Yamazaki N, Higashi T: A retrospective study of sentinel lymph node biopsy for skin cancer in Japan: Comparison with breast cancer and evaluation of factors related to its use. *Cancer Med*. 2023 Dec; 12(23):21364-21372. doi: 10.1002/cam4.6677. Epub 2023 Oct 30.
 23. Watanabe T, Rikitake R, Kakuwa T, Ichinose Y, Niino M, Mizushima Y, Ota M, Fujishita M, Tsukada Y, Higashi T: Time to Treatment Initiation for Six Cancer Types: An Analysis of Data from a Nationwide Registry in Japan. *World J Surg*. 2023 Apr; 47(4):877-886. doi: 10.1007/ s00268-022-06883-5. Epub 2023 Jan 6.
 24. Omura G, Yoshimoto S, Rikitake R, Eguchi K, Nakamizo M, Nibu K: Comparison of survival outcomes between adolescent and young adults and older adults with tongue squamous cell carcinoma: a nationwide database study using the head and neck cancer registry of Japan. *Int J Clin Oncol*. 2023 Feb;28(2):221-228. doi: 10.1007/ s10147-022- 02279-6. Epub 2022 Dec 15.
 25. Ichikawa M, Inada H, Katanoda K, Nakahara S. Trend in alcohol-related crashes before and after the introduction of mandatory breath testing among commercial truck drivers. *J Epidemiol*. 2023;33(11):556–561. doi:10.2188/jea.JE20220054
 26. 竹上 未紗. 【睡眠時無呼吸症候群(SAS)】 SAS の分類とその疫学. *糖尿病・内分泌代謝科* 57 巻 2 号 Page126-132
 27. 力武 諒子, 渡邊 ともね, 山元 遥子, 市瀬 雄一, 松本 公一, 新野 真理子, 松木 明, 伊藤 ゆり, 太田 将仁, 坂根 純奈, 東 尚弘, 若尾 文彦:がん診療連携拠点病院等における AYA 世代がん支援体制 2021 年の現況; AYA がんの医療と支援, 3(2), 40-46, 2023.
 28. 坂根 純奈, 伊藤 ゆり, 太田 将仁, 上田 育子, 力武 諒子, 渡邊 ともね, 山元 遥子, 市瀬 雄一, 新野 真理子, 松木 明, 東 尚弘, 若尾 文彦 :がん患者に対する苦痛のスクリーニングの現状—がん診療拠点病院等の指定要件に関する調査より;病院 82(9), 808-815, 2023
- (Others)
29. Inada H, Ichikawa M. Change in the incidence of fires after prohibiting sales of non-child-resistant lighters. *Fire Saf J*. 2023;141:103992. doi: 10.1016/j.firesaf.2023.103992 (Short communication)
 30. Ichikawa M, Hori A, Inada H, Tabuchi T. Intensified advertising of heated tobacco products in Japan: An apparent shift in marketing strategy. *Tob Control*. 2023;32(1):130. doi: 10.1136/tobaccocontrol-2021-056615 (Letter)
 31. No Difference in Quality, Cost for Patients Treated by Hospitalist MDs vs DOs. *JAMA*. 2023;329(24):2119. doi:10.1001/jama.2023.9932 2023 年 6 月 7 日
 32. Care by Osteopathic or Allopathic Hospitalists Leads to Similar Outcomes. *NEJM Journal Watch*. <https://www.jwatch.org/na56194/2023/06/22/care-osteopathic-or-allopathic-hospitalists-leads-similar> 2023 年 6 月 22 日

Social Medicine

2. Forensic Medicine, and Medical Informatics and Economics

Department of Forensic Medicine

Professor

Hirotarō Iwase, M.D., Ph.D.

Associate Professor

Yohsuke Makino, M.D., Ph.D.

Assistant Professor

Suguru Torimitsu, M.D., Ph.D.,

Project Assistant Professor

Go Inokuchi, M.D., Ph.D., Ayumi Motomura, M.D., Ph.D., Fumiko Chiba, M.D., Ph.D.,
Shigeki Tsuneya, M.D., Ph.D., Rutsuko Yamaguchi, M.P.H., M.D., Ph.D.

Homepage <http://ut-forensic.jp/>

Introduction and Organization

Associate Professor Kuniyoshi Katayama lectured “judicial medicine” in the University of Tokyo since 1881 before our department was founded as the first department of forensic medicine in Japan in 1889. He renamed “judicial medicine” to “forensic medicine” in 1891 since the department should cover legislation as well as general forensic practices. Dr. Katayama became the first professor of forensic medicine in Japan.

The 2nd Professor Sadanori Mita also founded the serological department (Department of Immunology at present). He studied the antigen-antibody reaction and discovered complement fixation reaction.

The 3rd Professor Tanemoto Furuhashi was very famous for ABO blood group genetics, and also contributed to the development of criminology. He autopsied several cases of historical crimes.

The 4th Professor Shokichi Ueno discovered a complex complement. He helped foundation of national police academy for death investigators.

The 5th Professor Toshiyuki Miki could not perform autopsy for four years due to the University of Tokyo strike. However, he left many achievements in the field of blood typing and paternity examination.

The 6th Professor Ikuo Ishiyama encouraged forensic pathology. He also introduced DNA fingerprinting and PCR technique in the forensic practices.

The 7th Professor Takehiko Takatori studied the biochemical changes of the lipid in cadavers. He dissected five victims of sarin subway attacks in Tokyo and identified sarin in tissue by a sophisticated method.

The 8th Professor Ken-ichi Yoshida studied the molecular mechanism of ischemic heart disease and sudden cardiac death.

Hirotarō Iwase has been directing our department since 2014 as the 9th Professor. In order to reconstruct the field of forensic medicine as the attractive one, six sections (forensic pathology, clinical forensic medicine, forensic toxicology, forensic radiology, forensic odontology, forensic genetics) have started in cooperation with Chiba University. We are preparing to teach practice and research for the future forensic pathologists.

Postmortem examination

The determination of precise cause of death is one of the most important practices at our department. We perform medico-legal autopsies for around 150

criminal cases in eastern part of Tokyo every year. We also perform post-mortem CT at the request of police.

In medico-legal autopsy, we usually examine various tests such as the pathological, alcohol, toxicological, and blood type tests. Finally, forensic pathologists in our department diagnose the cause of death. Expert opinions express the cause of death and forensic judgment for each case.

Infection control in dissection was still a hot topic. With the introduction of the laminar-flow autopsy table following the seismic retrofitting carried out in 2019, our department has become possible to accept SARS-CoV-2-infected bodies. In 2020, we have newly introduced our own real-time PCR system in our laboratory, since then, we had conducted a SARS-CoV-2 PCR test in all cases until the pandemic ended. This year, we had several COVID-19 cases, and autopsies were performed with PAPRs (powered air-purifying respirators) in some cases.

Education

As for under-graduate education, our department provides lectures for the 4th year medical students, Free Quarter training course for the 2nd-4th year medical students, and Elective Clerkship learning for the 6th year medical students.

The lectures consist of forensic pathology, clinical forensic medicine, forensic toxicology, forensic radiology, forensic odontology and forensic genetics. In the Free Quarter training course, students experience laboratory practices (toxicology and histology) or research. In the Elective Clerkship learning, each student experiences the process from autopsy to presentation of expert opinion.

In addition, students of school of public health and (undergraduate & graduate) law school are provided with somewhat practical lectures with exercises. We have provided opportunity for PhD students of School of Health Science, and master course of Medical Science.

Research

In cooperation with other universities including Chiba University, Tokyo Medical and Dental University, and International University of Health and Welfare, researches in 6 sections (forensic pathology,

clinical forensic medicine, forensic toxicology, forensic radiology, forensic odontology and forensic genetics) have proceeded.

1. Forensic Pathology

We conduct research aimed at improving the accuracy of cause-of-death diagnosis and epidemiological studies related to cause-of-death investigation. For example, we are trying angiographic 3D-CT and vascular endoscopy in the search for coronary arteries and cerebral basilar arteries. We are also conducting research on diatoms in order to improve the diagnosis of drowning. Additionally, we are trying to conduct a comparative study of the cause-of-death investigation systems in Tokyo and Chiba prefectures.

2. Clinical Forensic Medicine

Clinical forensic medicine is an academic field that collaborates with various clinical departments to examine a living body that may have been subjected to some form of invasion to determine whether or not an invasion has occurred, and to devise measures to prevent accidents based on information obtained from the accumulation of cause-of-death information. Currently, in collaboration with pediatricians, we are conducting research on the accumulation and analysis of pediatric deaths and their application to prevention. As part of this effort, the Chiba Prefecture Child Death Review (CDR) Study Group has been established in cooperation with Chiba University. In addition, we are also conducting research on bone strength to gain knowledge that will be useful in the evaluation of abuse.

3. Forensic Toxicology

Using LC/MS/MS, LC/QTOF-MS, etc., we are conducting research on detection methods targeting a large number of drugs, including cyanide compounds and dangerous drugs. Animal studies on postmortem drug redistribution had also been conducted. In collaboration with the National Research Institute of Police Science and others, we are also conducting epidemiological studies on drug detection in traffic accident fatalities.

4. Forensic Odontology

Studies are being conducted to examine the usefulness of drug analysis, DNA testing, CT testing, etc., from teeth and palatine and mandible bones for age estimation and other utilities.

5. Forensic Genetics

We are trying research to search for disease genes in cases of sudden death. We are also conducting research on the detection of novel coronavirus genes in cadavers.

6. Forensic Radiology

Using 3D-CT, we are studying the possibility of estimating the stature, sex, and age of the deceased based on bone length and morphology. We are also conducting research on the benefits and risks of postmortem imaging to determine the cause of death. In collaboration with the other universities, we are also studying the characteristics of postmortem CT in COVID-19 deaths.

Publications

1. Saitoh H, Takeyama M, Moriya T, Yusa K, Minegishi S, Torimitsu S, Chiba F, Hoshioka Y, Nagasawa S, Iino M, Sakurada K, Iwase H, Tokanai F. Usefulness of powdered crown of mandibular first premolars in birth year estimation by radiocarbon dating. *J Forensic Leg Med.* 2023; 100: 102607.
2. Yoshida M, Hoshioka Y, Makino Y, Yamagishi Y, Nagasawa S, Chiba F, Yamaguchi R, Inokuchi G, Iwase H. Fatal cocaine body packer syndrome depicted on antemortem and postmortem CT: A case report. *Forensic imaging.* 33(11),2023
3. Saitoh H, Sakai-Tagawa Y, Nagasawa S, Torimitsu S, Kubota K, Hirata Y, Iwatsuki-Horimoto K, Motomura A, Ishii N, Okaba K, Horioka K, Abe H, Ikemura M, Rokutan H, Hinata M, Iwasaki A, Yasunaga Y, Nakajima M, Yamaguchi R, Tsuneya S, Kira K, Kobayashi S, Inokuchi G, Chiba F, Hoshioka Y, Mori A, Yamamoto I, Nakagawa K, Katano H, Iida S, Suzuki T, Akitomi S, Hasegawa I, Ushiku T, Yajima D, Iwase H, Makino Y, Kawaoka Y. High titers of infectious SARS-CoV-2 in corpses of patients with COVID-19. *Int J Infect Dis.* 2023 Apr; 129: 103-109. doi: 10.1016/j.ijid.2023.01.046. Epub 2023 Feb 7. PMID: 36754229; PMCID: PMC9902281.
4. Torimitsu S, Nishida Y, Takano T, Yajima D, Inokuchi G, Makino Y, Motomura A, Chiba F, Yamaguchi R, Hoshioka Y, Iwase H. Statistical analysis of the thickness and biomechanical properties of Japanese children's skulls. *Forensic Sci Int.* 2023; 344: 111580.
5. Nagasawa S, Yamaguchi R, Chiba F, Torimitsu T, Iwase H. Identification, measurement, and evaluation of blood concentrations of insulin glargine and insulin lispro by UPLC-MS-MS in a dead body suspected of insulin overdose. *J Forensic Sci.* 2023; 69: 704-710.
6. Torimitsu S, Nishida Y, Yajima D, Inokuchi G, Makino Y, Motomura A, Chiba F, Yamaguchi R, Hoshioka Y, Iwase H. Statistical analysis of biomechanical properties and size of the sternum and its fracture risk in a Japanese sample. *Leg Med (Tokyo).* 2023; 62: 102242.
7. Torimitsu S, Chiba F, Makino Y, Yamaguchi R, Tsuneya S, Kira K, Yajima D, Inokuchi G, Motomura A, Hoshioka Y, Saitoh H, Iwase H. Age estimation using aortic measurements in a contemporary Japanese population. *Australian Journal of Forensic Sciences.* 2023; 1-11.
8. Unuma K, Sato H, Wen S, Makino Y, Hirakawa A, Uemura K. The proportion of false-positives in positive Seratec® prostate-specific antigen SemiQuant test results in postmortem screening for seminal fluid. *Leg Med (Tokyo).* 2023 May; 62:102243. doi: 10.1016/j.legalmed.2023.102243. Epub 2023 Mar 21. PMID: 36965350.
9. Kobayashi S, Makino Y, Torimitsu S, Yamaguchi R, Chiba F, Tsuneya S, Iwase H. Age estimation by evaluating median palatine suture closure using postmortem CT. *Int J Legal Med.* 2023 Jul; 137(4):1097-1107. doi: 10.1007/s00414-023-02994-3. Epub 2023 Apr 19. PMID: 37074412.
10. Kobayashi S, Makino Y, Torimitsu S, Mizuno S, Yamaguchi R, Chiba F, Tsuneya S, Iwase H. Age estimation by palatal suture using modified Kamijo's method. *Forensic Sci Int.* 2023 Jul; 348: 111706. doi: 10.1016/j.forsciint.2023.111706. Epub 2023 Apr 21. PMID: 37137211.

11. Hirata Y, Makino Y, Iida S, Katano H, Nagasawa S, Rokutan H, Hinata M, Iwasaki A, Yasunaga Y, Abe H, Ikemura M, Motomura A, Kira K, Kobayashi S, Tsuneya S, Torimitsu S, Yamamoto I, Nakagawa K, Hasegawa I, Akitomi S, Yajima D, Ushiku T, Saitoh H, Suzuki T, Iwase H. Analysis of COVID-19 in tissues acquired by minimally invasive autopsy in out-of-hospital deaths with postmortem degeneration. *Jpn J Infect Dis.* 2023 Sep 22;76(5):302-309. doi: 10.7883/yoken.JJID.2023.140. Epub ahead of print. PMID: 37394459.
12. Hirata Y, Katano H, Iida S, Mine S, Nagasawa S, Makino Y, Motomura A, Ozono S, Sato Y, Sekizuka T, Kuroda M, Yamaguchi R, Inokuchi G, Torimitsu S, Akitomi S, Yajima D, Saitoh H, Suzuki T, Iwase H. Genomic analysis of SARS-CoV-2 in forensic autopsy cases of COVID-19. *J Med Virol.* 2023 Aug;95(8):e28990. doi: 10.1002/jmv.28990. PMID: 37537838.
13. Kihara Y, Makino Y, Yokoyama M, Chiba F, Tanaka A, Nakayama SMM, Hayama SI, Ishizuka M, Nolte KB, Iwase H. X-ray analytic microscopy with CT-guided sample extraction to analyze potential projectile fragments in a dead serow. *Leg Med (Tokyo).* 2023 Jul;63:102257. doi: 10.1016/j.legalmed.2023.102257. Epub 2023 Apr 11. PMID: 37068342.
14. Unuma K, Tomomasa D, Noma K, Yamamoto K, Matsuyama TA, Makino Y, Hijikata A, Wen S, Ogata T, Okamoto N, Okada S, Ohashi K, Uemura K, Kanegane H. Case Report: Molecular autopsy underlie COVID-19-associated sudden, unexplained child mortality. *Front Immunol.* 2023 Apr 18;14:1121059. doi: 10.3389/fimmu.2023.1121059. PMID: 37143668.
15. Makino Y, Kojima M, Inokuchi G, Motomura A, Arai N, Inoue H, Kabasawa H, Iwase H, Yajima D. Two medicolegal autopsy cases of multi-nodular and vacuolating neuronal tumor revealed by postmortem MRI. *Leg Med (Tokyo).* 26: 102342, 2023.
16. Wen S, Unuma K, Inaji M, Makino Y, Nagano S, Harada K, Arai N, Uemura K. Casereport: Fatal ischemic stroke induced by unruptured traumatic intracranial vertebral artery dissection. *Front Neurol.* 2023 Sep 12;14:1202698. doi: 10.3389/fneur.2023.1202698. PMID: 37780720; PMCID: PMC10536137.
17. Tsuneya S, Yoshida M, Hoshioka Y, Chiba F, Inokuchi G, Torimitsu S, Iwase H. Relevance of diatom testing on closed organs of a drowned cadaver who died after receiving treatment for 10 days: A case report. *Leg Med (Tokyo).* 2023; 60:102168.
18. Tsuneya S, Nakajima M, Makino Y, Torimitsu S, Yamaguchi R, Iwase H. Effect of ethanol on the diatom test using nitric acid or sodium hypochlorite. *Leg Med (Tokyo).* 2023; 61: 102190.
19. Hirata Y, Iida S, Arashiro T, Nagasawa S, Saitoh H, Abe H, Ikemura M, Makino Y, Sawa Y, Iwase H, Ushiku T, Suzuki T, Akitomi S. Impact of the COVID-19 pandemic on pathological autopsy practices in Japan. *Pathol Int.* 2023; 73:120-126.
20. Yamagishi Y, Inokuchi G, Hoshioka Y, Nagasawa S, Iwase H, Ogra Y. Identification of postmortem paliperidone metabolite in human blood by LC-Q-Orbitrap-MS. *Journal of Analytical Toxicology* 2023; bkad033.
21. Iwatsuki-Horimoto K, Ueki H, Ito M, Nagasawa S, Hirata Y, Hashizume K, Ushiwata K, Iwase H, Makino Y, Ushiku T, Akitomi S, Imai M, Saitoh H, Kawaoka Y. SARS-CoV-2 Transmission from Virus Infected Dead Hamsters. *mSphere.* 2023; 21:e0041122.
22. Takahashi K, Horiai S, Yamagishi Y, Nagasawa S, Iwase H, Ogra Y. Biotransformation of se-methylselenocysteine into volatile selenocompounds by bacteria isolated from rat gut microflora. *J Funct Foods.* 2023;107:105687.

Department of Biomedical Informatics

Professor

Kazuhiko Ohe, M.D.,Ph.D.

Associate Professor

Kayo Waki, M.D.,Ph.D. Yoshimasa Kawazoe, M.D.,Ph.D.

Takeshi Imai, Ph.D.

Lecturer

Shinichiro Yokota, PHN,RN,Ph.D., Hidenao Atarashi BMET, Ph.D.

※The following information is the same as that of the previous year for certain reasons.

Homepage <http://www.m.u-tokyo.ac.jp/medinfo/>

Introduction and Organization

We aim to transform medical care and contribute to society by applying the following methods to clinical medicine and medical management; development of basic methods that can be applied to medical information systems in the interdisciplinary field between medicine and informatics, development and construction of basic information environments related to medical information, practical research on medical information systems, and knowledge in these areas.

Keywords for the fields covers medical information system, next-generation electronic medical records, medical information network, virtual medical information environment, computer representation and standardization of medical concepts, medical knowledge engineering, hospital information epidemiology, evaluation of medical quality, clinical information engineering, privacy protection and encryption, Information security, medical analysis, hospital management analysis, medical safety management. The professor concurrently supervise as the director of the Department of Planning and Information Management at the University of Tokyo Hospital, which is united with this department.

The Department of Planning and Information Management is a place where the medical information system is used to analyze information related to the future plan of the University Hospital.

Our department began in 1983 when the Department of Central Information of the University of Tokyo Hospital, as the National University Hospitals, was formally established, and the medical informatics doctoral course was established in the Graduate School of Basic Medicine I of the Graduate School of Medicine, the University of Tokyo at that time. The first professor was Shigekoto Kaihara (deceased) who established medical informatics in Japan, and the current professor is the second generation. In 1997, when the University of Tokyo became a graduate school, it became the current Department of Social Medicine, Medical Information Economics, and the one professor and one associate professor, who belonged to the Department of Central Information of the University of Tokyo Hospital, moved to full-time staffs of the graduate school.

Teaching activities

In 2022, the faculty composition, including the

hospital staff, is 1 professor (Ohe), 1 associate professor (Waki), 2 lecturers (Atarashi, Yokota), 2 assistant professor (specially appointed lecturer (hospital)). (Doi, Ida), 4 assistant professors (Nagae, Mori, Seki), and 2 special assistant professors (Miyake, Kubota). In addition to these, Associate Professor 1 (Disease and Biotechnology Center) (Imai) and Specially Appointed Associate Professor 1 (Endowed Department of Medical AI Development) (Kawazoe) are also in charge of this course. In the doctoral course of medicine, we educate graduate students in medical informatics, and in the public health medicine major (professional master's course), we are in charge of medical information systems (medical information system lecture 15 units 2 credits, practical training 30 units 1 credit), every year About 10 students are taking elective courses.

The lecture course is 1) Overview of information technology infrastructure and systems related to medical computerization policies in Japan and overseas, 2) Hospital information systems, electronic medical record systems, and standardization of medical information. 3) Security management of medical personal data and information networks. 4) Medical information database—National DB and Sentinel DB, 5) Mobile IT medical care, lifestyle disease management and IT, 6) Knowledge and information handling in medical care, language processing, 7) Open data handling and discussion. was the content.

Practical training consists of 1) data creation, conversion, and Internet basic technical training, 2) database design and database operation: learning a series of basic operations of relational databases based on medical sample data. Acquire the basic technology of data interconversion.3) Learn to convert data into standardized code.4) Create a database, extract and convert data suitable for a given task by creating a program, and conduct research.

It is also a health and medical informatics cooperative course for the Department of Health Science and Nursing, and is in charge of the health science and nursing doctoral course (three years). If desired, we also accept students in the master's course of medical science, and are mainly in charge of Associate Professor Takeshi Imai (Center for Disease Biotechnology), who is also in charge of the

department. In the master's program in medical science, Imai was in charge of one lecture on medical informatics and clinical medical ontology. Our department has an educational system that allows students to obtain degrees such as Doctor of Medicine, Master of Public Health Medicine, Doctor of Health Science, and Master of Medical Science. There was 1 master of medical science and 1 master of public health medicine. At the Faculty of Medicine, staffs were in charge of 5 lectures on medical informatics in M2.

In the Ministry of Education, Culture, Sports, Science and Technology's medical data human resource development project "Development Project of Medical Real World Data Utilization Human Resource" adopted in 2019, the first batch of students will be accepted from May 2020. Assistant professors were in charge, and lectures and practical training were mainly held on Saturdays as adult education courses. Details are available at <https://www.med-rwd.jp/>.

Research activities

Main research areas: 1) Applied research on hospital information systems and medical information systemization represented by electronic medical records, 2) New medical knowledge extraction and medical economics targeting electronic medical records and hospital information system databases 3) Standardization of descriptions of clinical medical terminology and concepts and research on structured knowledge representation methods 4) Basic research on information systems for clinical research 5) Personal information protection and security in medical information systems 6) Research on lifestyle-related disease management using mobile devices. Representative research themes are as follows.

Research and development of a standardization platform for medical information and its utilization, automatic information collection of hospital wards using FHIR standard specifications, basic research on medical text analysis for natural language processing, research on fall risk prediction model and evaluation for inpatients, AI-based automatic finding classification of renal pathological images,

development of clinical support systems based on clinical guidelines, e-Phenotyping, etc. In addition, we are carrying out many industry-university collaborative researches with clinical research on lifestyle-related diseases and self-management of health using mobile devices such as smartphones as the main research theme.

As social activities, the Ministry of Health, Labor and Welfare's study group on various medical information policies (Medical Information Standardization Committee, ICD Special Committee), the Japanese Association of Medical Sciences Terminology Management Committee, the Social Insurance Medical Fee Payment Fund Standard Injury Name Master Review Committee, International Several staff members play important roles in WG2 of the Organization for Standardization ISO/TC215 (Medical Information Standardization Committee), the Ministry of Health, Labor and Welfare/PMDA medical information database infrastructure development project MID-NET, and research on the utilization of the national health insurance claim database NDB.

References

1. Kawazoe Y, Shimamoto K, Yamaguchi R, Nakamura I, Yoneda K, Shinohara E, Shintani-Domoto Y, Ushiku T, Tsukamoto T, Ohe K. Computational Pipeline for Glomerular Segmentation and Association of the Quantified Regions with Prognosis of Kidney Function in IgA Nephropathy. *Diagnostics*. 2022;12(12): 2955.
2. Takeuchi A, Yokota S, Tomotaki A, Fukahori H, Shimpuku Y, Yoshinaga N. Relationship between Research Activities and Individual Factors among Japanese Nursing Researchers during the COVID-19 Pandemic. *PLOS ONE*. 2022;17(8): e0271001.
3. Hayakawa J, Seki T, Kawazoe Y, Ohe K. Pathway Importance by Graph Convolutional Network and Shapley Additive Explanations in Gene Expression Phenotype of Diffuse Large B-cell Lymphoma. *PLOS ONE*. 2022;17(6): e0269570.
4. Masukawa K, Aoyama M, Yokota S, Nakamura J, Ishida R, Nakayama M, Miyashita M. Machine Learning Models to Detect Social Distress, Spiritual Pain, and Severe Physical Psychological Symptoms in Terminally Ill Patients with Cancer from Unstructured Text Data in Electronic Medical Records. *Palliative Medicine*. 2022;36(8): 1207-1216.
5. Tomotaki A, Iwamoto T, Yokota S. Research Types and New Trends on the Omaha System Published in English and Japanese from 2012 to 2019: A Scoping Review. *CIN: Computers, Informatics, Nursing*. 2022;40(8): 531-537.
6. Kawai Y, Waki K, Yamaguchi S, Shibuta T, Miyake K, Kimura S, Toyooka T, Nakajima R, Uneda K, Wakui H, Tamura K, Nangaku M, Ohe K. The Use of Information and Communication Technology-Based Self-management System DialBeticsLite in Treating Abdominal Obesity in Japanese Office Workers: Prospective Single-Arm Pilot Intervention Study. *JMIR Diabetes*. 2022; 7(4): e40366.
7. Kondo M, Okitsu T, Waki K, Yamauchi T, Nangaku M, Ohe K. Effect of Information and Communication Technology-Based Self-management System DialBeticsLite on Treating Abdominal Obesity in the Specific Health Guidance in Japan: Randomized Controlled Trial. *JMIR Formative Research*. 2022;6(3): e33852.
8. Kurasawa H, Waki K, Chiba A, Seki T, Hayashi K, Fujino A, Haga T, Noguchi A, Ohe K. Treatment Discontinuation Prediction in Patients With Diabetes Using a Ranking Model: Machine Learning Model Development. *JMIR Bioinform Biotech*. 2022;3(1): e37951.
9. Sankoda A, Waki K, Yamaguchi S, Mieno M, Nangaku M, Yamaguchi T, Ohe K. Effect of Digital Health Among People With Type 2 Diabetes Mellitus During the COVID-19 Pandemic in Japan. *Journal of Diabetes Science and Technology*. 2022;16(1): 256-258.

Internal Medicine

1. Medicine I

Department of Cardiovascular Medicine

Professor

Issei Komuro, M.D., Ph.D.

Associate Professor

Hatano Masaru, M.D., Ph.D. (Advanced Medical Center for Heart Failure)

Lecturer

Hiroyuki Morita, M.D., Ph.D. Hiroshi Akazawa, M.D., Ph.D.

Eiki Takimoto, M.D., Ph.D.

Hospital Lecturer

Norifumi Takeda, M.D., Ph.D. Satoshi Kodera, M.D., Ph.D.

※The following information is the same as that of the previous year for certain reasons.

Homepage <https://cardiovasc.m.u-tokyo.ac.jp/>

Introduction and Organization

The Department of Cardiovascular Medicine was established in 1998 by regrouping cardiologists of five previous internal medical departments. After Yoshio Yazaki, the first professor, and Ryozi Nagai, the second professor, the present professor Issei Komuro was elected in August, 2012. Our department comprises one professor, one associate professor, 3 lecturers, 2 hospital lecturers, 16 research assistants, 7 staff members, and 41 graduate school students.

Clinical activities

The Department of Cardiovascular Medicine is actively involved in clinical medicine, basic research and teaching. Not only do we have the most advanced equipment and facilities (e.g., 24-hour cardiac care unit), but our personnel are also highly trained to be knowledgeable and experts in modern methods of diagnosis and treatment. Especially, we make a special effort to treat patients with severe heart failures. As a teaching and research hospital, we also emphasize the

development and integration of new treatment methods if they may be beneficial to patients.

In 2022, a total of 1,777 patients were newly admitted to our hospital ward of 57 beds. The average duration of hospitalization was 11.2 days.

Because we are an authorized facility for heart transplantation, the use of left ventricular assist device in cases of severe heart failure has been increasing. In 2006, the first patient with heart failure from our department underwent a heart transplant procedure at the Department of Cardiovascular Surgery. In 2022, 18 patients underwent heart transplant (total 189 cases). In March 2014, our facility was also authorized to perform lung transplantation. Coronary angiography was performed in 1,864 patients, of which 417 patients underwent percutaneous coronary interventions. CT coronary angiography and cardiovascular MRI were performed in 636 and 176 patients, respectively. With regard to arrhythmias, there were 257 cases of catheter ablation, 99 cases of implantation or replacement of pacemakers and other specialized pacemaker devices, including 13 cases of implantation or replacement of

implantable cardioverter-defibrillator and 7 cases of implantation or replacement of a cardiac resynchronization device.

Out-patient clinics are available as a specialized department and as part of the Department of Medicine. Out-patient clinics are open in the mornings and afternoons from Monday to Friday, and approximately 182.5 patients visited each day. The disease profile includes ischemic heart disease, heart failure, arrhythmia, hypertension and peripheral artery disease. There are special outpatient clinics for advanced heart failure, ischemic heart disease, pulmonary hypertension, congenital heart disease, valvular heart disease, arrhythmia, Marfan syndrome, myocarditis, cardiac amyloidosis, onco-cardiology, and cardiac rehabilitation. The department is also focused on acute cases of coronary heart disease and aortic disease, as emergent catheterization is available on a 24-hour basis.

Education

We have a particular interest in teaching not only medical students but also residents, who are important for the future of cardiovascular medicine. The courses available at the medical school include clinical lectures and clinical clerkships. In clinical clerkship, three students are placed under the guidance of one research associate, which enables teaching in small groups. Specialized groups provide practical lectures. Residents are educated through specialized group conferences, grand rounds, and clinical conferences.

Research activities

From a research perspective, our interests include all fields of cardiovascular medicine, ranging from molecular biology to clinical research, including genomics. Importantly, our research interests are aimed at facilitating new diagnostic and treatment methods for cardiovascular diseases. Our areas of interest include the following:

1. Cardiac hypertrophy and heart failure: multiomics analyses of pathogenic mechanisms and development of novel therapies (e.g., gene therapy)
2. Interplay between organs, cells, and molecules in chronic inflammation
3. Genetic analysis of inherited cardiomyopathy
4. Experiments on pathophysiology of cardiomyopathy using human iPS cells
5. Investigation of disease pathophysiology and development of novel therapies (severe heart failure, cardiac transplantation, congenital heart disease, etc.)
6. New treatments for structural heart disease
7. Diagnosis and treatment of Marfan syndrome and adult congenital heart disease
8. New treatments for pulmonary hypertension
9. New treatments for congenital heart disease
10. Aerobic threshold and cardiac rehabilitation
11. Imaging techniques (echocardiography, MRI, CT, and SPECT) in cardiovascular diseases
12. Epidemiology and prevention of cardiovascular disease
13. Artificial Intelligence in Cardiology

Publications (2022)

1. Adachi Y, Ueda K, Nomura S, Ito K, Katoh M, Katagiri M, Yamada S, Hashimoto M, Zhai B, Numata G, Otani A, Hinata M, Hiraike Y, Waki H, Takeda N, Morita H, Ushiku T, Yamauchi T, Takimoto E and Komuro I. Beiging of perivascular adipose tissue regulates its inflammation and vascular remodeling. *Nat Commun* 13:5117, 2022.
2. Bujo S, Amiya E, Maeda MH, Ishida J, Hatano M, Ishizuka M, Uehara M, Oshima T, Kojima T, Nakanishi K, Daimon M, Shimizu J, Toda T and Komuro I. The effect of immunosuppressive therapy on cardiac involvements in anti-mitochondrial antibody-positive myositis. *ESC Heart Fail* 9:4112-4119, 2022.
3. Fukui A, Kaneko H, Okada A, Yano Y, Itoh H, Matsuoka S, Morita K, Kiriya H, Kamon T, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Nakamura S, Nishiyama A, Node K, Yokoo T, Nangaku M, Yasunaga H and Komuro I. Semiquantitative assessed proteinuria and risk of heart failure: analysis of a nationwide epidemiological database. *Nephrol Dial Transplant* 37:1691-1699, 2022.
4. Ieki H, Ito K, Saji M, Kawakami R, Nagatomo Y, Takada K, Kariyasu T, Machida H, Koyama S, Yoshida H, Kurosawa R, Matsunaga H, Miyazawa

- K, Ozaki K, Onouchi Y, Katsushika S, Matsuoka R, Shinohara H, Yamaguchi T, Kodera S, Higashikuni Y, Fujiu K, Akazawa H, Iguchi N, Isobe M, Yoshikawa T and Komuro I. Deep learning-based age estimation from chest X-rays indicates cardiovascular prognosis. *Commun Med (Lond)* 2:159, 2022.
5. Itoh H, Kaneko H, Okada A, Suzuki Y, Fujiu K, Matsuoka S, Michihata N, Jo T, Nakanishi K, Takeda N, Morita H, Node K, Di Tullio MR, Homma S, Yasunaga H and Komuro I. Age-Specific Relation of Cardiovascular Health Metrics With Incident Cardiovascular Disease. *Am J Cardiol* 177:34-39, 2022.
6. Kamon T, Kaneko H, Itoh H, Okada A, Matsuoka S, Kiriya H, Fujiu K, Morita K, Michihata N, Jo T, Takeda N, Morita H, Nakamura S, Node K, Yasunaga H and Komuro I. Sex Difference in the Association between Lipid Profile and Incident Cardiovascular Disease among Young Adults. *J Atheroscler Thromb* 29:1475-1486, 2022.
7. Kaneko H, Yano Y, Lee HH, Lee H, Okada A, Itoh H, Morita K, Fukui A, Fujiu K, Suzuki Y, Matsuoka S, Nakamura S, Michihata N, Jo T, Takeda N, Morita H, Yokoo T, Nishiyama A, Node K, Viera AJ, Muntner P, Oparil S, Kim HC, Yasunaga H and Komuro I. Medication-Naïve Blood Pressure and Incident Cancers: Analysis of 2 Nationwide Population-Based Databases. *Am J Hypertens* 35:731-739, 2022.
8. Kaneko H, Yano Y, Suzuki Y, Okada A, Itoh H, Matsuoka S, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Node K, Viera AJ, Lima JAC, Oparil S, Lam CSP, Carey RM, Yasunaga H and Komuro I. Reduction in blood pressure for elevated blood pressure/stage 1 hypertension according to the American College of Cardiology/American Heart Association guideline and cardiovascular outcomes. *Eur J Prev Cardiol* 29:1921-1929, 2022.
9. Ko T, Nomura S, Yamada S, Fujita K, Fujita T, Satoh M, Oka C, Katoh M, Ito M, Katagiri M, Sassa T, Zhang B, Hatsuse S, Yamada T, Harada M, Toko H, Amiya E, Hatano M, Kinoshita O, Nawata K, Abe H, Ushiku T, Ono M, Ikeuchi M, Morita H, Aburatani H and Komuro I. Cardiac fibroblasts regulate the development of heart failure via Htra3-TGF-beta-IGFBP7 axis. *Nat Commun* 13:3275, 2022.
10. Matsuoka S, Kaneko H, Kamon T, Suzuki Y, Yano Y, Okada A, Itoh H, Morita K, Fukui A, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Nakamura S, Yokoo T, Nishiyama A, Node K, Yasunaga H and Komuro I. Incorporation of Retinal Arteriolosclerosis into Risk Stratification of Blood Pressure Category According to the 2017 ACC/AHA Blood Pressure Guideline. *J Atheroscler Thromb* 29:1487-1498, 2022.
11. Matsuoka S, Kaneko H, Okada A, Morita K, Itoh H, Michihata N, Jo T, Takeda N, Morita H, Fujiu K, Nakamura S, Node K, Yasunaga H and Komuro I. Age Modified Relationship Between Modifiable Risk Factors and the Risk of Atrial Fibrillation. *Circ Arrhythm Electrophysiol* 15:e010409, 2022.
12. Nakanishi K, Daimon M, Yoshida Y, Ishiwata J, Sawada N, Hirokawa M, Kaneko H, Nakao T, Mizuno Y, Morita H, Di Tullio MR, Homma S and Komuro I. Blood pressure categorization and subclinical left ventricular dysfunction in antihypertensive medication-naïve subjects. *ESC Heart Fail* 9:1766-1774, 2022.
13. Nakayama A, Morita H, Sato T, Kawahara T, Takeda N, Kato S, Itoh H and Komuro I. Small Dense Low-Density Lipoprotein Cholesterol is a Potential Marker for Predicting Laser Treatment for Retinopathy in Diabetic Patients. *J Atheroscler Thromb* 29:678-691, 2022.
14. Numata G, Takimoto E, Kariya T, Adachi Y, Tokiwa H, Toyoda M, Mafune R, Saito Y, Nakamura S, Ueda K, Ikeda Y and Komuro I. A pacing-controlled protocol for frequency-diastolic relations distinguishes diastolic dysfunction specific to a mouse HFpEF model. *Am J Physiol Heart Circ Physiol* 323:H523-H527, 2022.
15. Suzuki Y, Kaneko H, Okada A, Matsuoka S, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Node K, Nangaku M, Yasunaga H and Komuro I. Kidney outcomes in patients with diabetes mellitus did not differ between individual sodium-glucose cotransporter-2 inhibitors. *Kidney Int* 102:1147-1153, 2022.
16. Suzuki Y, Kaneko H, Yano Y, Okada A, Itoh H, Ueno K, Matsuoka S, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Yokota I, Node K, Yasunaga H and Komuro I. Dose-dependent relationship of

blood pressure and glycaemic status with risk of aortic dissection and aneurysm. *Eur J Prev Cardiol* 29:2338-2346, 2022.

17. Suzuki Y, Kaneko H, Yano Y, Okada A, Matsuoka S, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Node K, Yasunaga H and Komuro I. Reduction in blood pressure for people with isolated diastolic hypertension and cardiovascular outcomes. *Eur J Prev Cardiol* 30:928-934, 2023.
18. Tsuji M, Kakuda N, Bujo C, Ishida J, Amiya E, Hatano M, Shimada A, Imai H, Shimada S, Kinoshita O, Yamauchi H, Ono M and Komuro I. Sarcopenia and risk of infection in adult heart transplant recipients in Japan. *ESC Heart Fail* 9:1413-1423, 2022.
19. Ueno K, Kamiya K, Kaneko H, Okada A, Itoh H, Fujiu K, Takeda N, Morita H, Michihata N, Jo T, Yasunaga H and Komuro I. Acute-Phase Initiation of Cardiac Rehabilitation for Short-Term Improvement in Activities of Daily Living in Patients Hospitalized for Acute Heart Failure. *J Cardiovasc Dev Dis* 9, 2022.
20. Ueno K, Kaneko H, Kamiya K, Itoh H, Okada A, Suzuki Y, Matsuoka S, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Ako J, Yasunaga H and Komuro I. Clinical utility of simple subjective gait speed for the risk stratification of heart failure in a primary prevention setting. *Sci Rep* 12:11641, 2022.
21. Yoshida Y, Nakanishi K, Daimon M, Hirose K, Ishiwata J, Kaneko H, Nakao T, Mizuno Y, Morita H, Di Tullio MR, Homma S and Komuro I. Aortic valve sclerosis and subclinical LV dysfunction in the general population with normal LV geometry. *Eur J Prev Cardiol*, 2022.

Department of Respiratory Medicine

Professor

Hidenori Kage, M.D.,Ph.D.

Lecturer

Akihisa Mitani, M.D.,Ph.D., Masanori Kawakami, M.D.,Ph.D.

Assistant Professor

Hirokazu Urushiyama, M.D.,Ph.D., Satoshi Noguchi, M.D.,Ph.D.

Yu Mikami, M.D., Ph.D., Kosuke Makita, M.D.,Ph.D.

Takahiro Ando, M.D., Ph.D. Kensuke Fukuda, M.D., Ph.D.

Hiroaki Ikushima, MD., PhD

Homepage <http://kokyuki.umin.jp/>

Introduction and Organization

The staff of the Department of Respiratory Medicine, Graduate School of Medicine, University of Tokyo, consists of 1 professor, 2 lecturers, and 8 assistant professors. At The University of Tokyo, affiliated hospitals and other institutions, approximately 70 members belong to the Department. At the University of Tokyo Hospital, 24 physicians belong to the Department.

Mortality from respiratory diseases such as primary lung cancer and COPD is expected to continue to increase, advancement of respiratory medicine research is necessary. We conduct basic and clinical research for a wide variety of respiratory disorders including primary lung cancer, COPD, asthma and interstitial lung diseases. We have focused on molecular mechanisms underlying the pathogenesis of lung disorders. Our research goal is to develop novel diagnostic and therapeutic modalities for better management of these pulmonary diseases.

Clinical activities

The Department of Respiratory Medicine is responsible for out-patient care as well as care of in-patients (35 patients on average) on the 13th floor of the hospital ward A at the University of Tokyo Hospital. We have two teams consisting of junior residents, two fellows, and an experienced attending.

In-patients are mostly admitted for primary lung cancer. Other diseases include respiratory infections, interstitial pneumonia, and COPD. Many patients with primary lung cancer also have co-existing interstitial pneumonia or COPD. There are many emergency visits and admissions from pneumonia, respiratory failure due to exacerbation of COPD or interstitial pneumonia, progression of lung cancer, etc. In cases of severe respiratory failure such as severe pneumonia and ARDS, we provide ventilatory support in collaboration with the ICU staff.

A specialized clinical conference for respiratory disease has been held once a week since the late 1990s, where staff from our department, Department of Thoracic Surgery, and Department of Radiology join and discuss together to determine the best diagnostic

and therapeutic approach to individual patients. This conference has been highly appreciated as a prototype of Cancer Board of the University of Tokyo Hospital, and, is now held as Respiratory Cancer Board. This conference is still one of the most frequently held Cancer Board at our hospital. Our department contributes to the pre- and post-surgical evaluation of respiratory functions, and also provides consultation on respiratory problems from almost every department at our hospital.

Together with the Department of Infectious Disease, we are responsible for taking care of COVID patients and infection control measures. We supervise the clinical teams that take care of inpatients with moderate COVID-19, make decisions on PCR testing and infection prevention practices, and run the fever clinic for patients who visit our hospital on a regular basis.

At present, primary lung cancer is the leading cause of cancer death, and is one of the major medical and social problem to be overcome. Recently, the remarkable effectiveness of molecular-targeted therapies in primary lung cancer attracted much attention in both basic science and clinical practice. Pneumonia is the 3rd leading cause of all deaths when combined with aspiration pneumonia, and COPD is also a major cause of death. No effective therapeutic modalities are currently available for many respiratory diseases. For example, mortality of acute respiratory distress syndrome (ARDS) is extremely high despite intensive care using currently available tools. Idiopathic pulmonary fibrosis is a progressive and fatal inflammatory and fibrotic disorder of the lung parenchyma, and only a few medications are currently available to treat the disease. Our focus is to develop a novel and potential therapeutic approach to these diseases.

Total numbers of in-patients in 2022

1. Primary lung cancer	375
2. Abnormal lung shadows	48
3. Interstitial pneumonia	61
4. Respiratory infections	58
5. Non-tuberculous mycobacterial infections	17
6. Other cancers	15

7. Pneumothorax	1
8. COPD	10
9. Others	29

A weekly chart round and professor's round are scheduled every Tuesday afternoon.

A specialized clinical conference for patients with respiratory diseases is held as Respiratory Cancer Board every Thursday evening, together with thoracic surgeons and radiologists. At this conference, radiological diagnosis, indication of CT-guided biopsy and thoracoscopic biopsy, and treatment strategies not only about thoracic malignancies but also other respiratory diseases are discussed, making it possible to give the best care to every patient.

Teaching activities

For medical school education, our department takes part in systematic lectures and specific learning for diagnosis and treatment of respiratory diseases for the 4th year medical students, clinical clerkship for 5th year medical students, and clinical lectures for 5th and 6th year medical students. During elective clerkship for 5th year students, students visit and learn from one of several leading affiliated hospitals in Tokyo.

During systematic lectures, the concept, pathogenesis, pathology, diagnosis, and treatment of common respiratory diseases are comprehensively presented. During clinical lectures, we present clinical cases of important diseases such as primary lung cancer and pneumothorax, and discuss several important points on the diagnostic evaluation and treatment in collaboration with the Faculty of the Department of Thoracic Surgery. Recent major advances in the relevant fields are also reviewed.

During clinical clerkship, each student, as a member of medical care team, has opportunities to experience the daily clinical care with residents and fellows as well as with the faculty. Each student learns how to perform a medical interview, perform physical exams and make plans for diagnosis and treatment. Respiratory specialists provide lecture on chest X-ray as an essential element in clinical clerkship, which is highly popular among the students. Elective clerkship during the 5th year of the educational program is

designed to facilitate the exposure to a wide range of clinical practice both at The University of Tokyo Hospital and at one of the affiliated hospitals for two weeks each (although COVID-19 pandemic made the latter unavailable in 2021). Several lectures on respiratory diseases are also provided.

As for post-graduate education, respiratory physicians (fellows and one attending) assemble a team with residents, and provide medical care for patients with various respiratory diseases. Under these process, residents acquire knowledge and skills required for diagnosis and treatment of respiratory diseases. Seminars on important themes such as medical treatment of lung cancer, diagnostic chest imaging, etc. are held at regular intervals.

Research

Our department conduct basic and clinical research for various respiratory disorders including primary lung cancer, COPD, asthma, interstitial pneumonia, and respiratory infection. Epidemiological, clinical, cellular, and molecular techniques are utilized for the elucidation of pathogenic mechanisms and for the development of novel diagnostic and therapeutic modalities in respiratory medicine. Postgraduate students as well as faculty members study genetic and epigenetic alterations in lung cancer, cell biology using airway epithelial cells, fibroblast and smooth muscle cells, both in collaboration with the Faculty of the Department of Thoracic Surgery. Genetically engineered mice are also used as disease models. These results have been presented and published in scientific meetings and peer-reviewed journals. Our main research projects are as follows.

- Search for diseases-susceptibility genes and elucidation of their pathophysiological roles in respiratory diseases
- Analysis of disease-models using genetically engineered mice
- Analysis of DNA methylation, histone modification and miRNA in lung cancer
- Search for previously unidentified oncogenic driver mutations in lung cancer and elucidation of resistant mechanisms to molecular-targeted drugs
- Analysis of functional alterations of airway epithelial cells and fibroblasts in relation to tissue repair and remodeling, e.g., epithelial-mesenchymal transition, and the roles of various cytokines and chemokines, in asthma and COPD
- Detection of small airway disease using impulse oscillometry and its clinical application
- Search for predictive factors for responses to chemotherapy in malignancy including lung cancer
- Epidemiological study of respiratory diseases, using Diagnosis Procedure Combination database.

Takahide Nagase is a GOLD Assembly member.

References

1. Matsumoto Y, Kage H, Morota M, Zokumasu K, Ando T, Maemura K, Watanabe K, Kawakami M, Hinata M, Ushiku T, Nakajima J, Nagase T. Integrin alpha 2 is associated with tumor progression and postoperative recurrence in non-small cell lung cancer. *Jpn J Clin Oncol*. 2023 Jan 6;53(1): 63-73.
2. Nakagawa N, Yamamoto S, Hanai A, Oiwa A, Arao H. Exercise intervention for the management of chemotherapy-induced peripheral neuropathy: a systematic review and network meta-analysis. *Front Neurol*.
3. Mizuno S, Ikegami M, Koyama T, Sunami K, Ogata D, Kage H, Yanagaki M, Ikeuchi H, Ueno T, Tanikawa M, Oda K, Osuga Y, Mano H, Kohsaka S. High-Throughput Functional Evaluation of MAP2K1 Variants in Cancer. *Mol Cancer Ther* 2023;22:227-239
4. Kimura Y, Jo T, Inoue N, Suzukawa M, Tanaka G, Kage H, Kumazawa R, Matsui H, Fushimi K, Yasunaga H, Matsui H. Association Between Systemic Corticosteroid Use and Mortality in Patients with Epiglottitis. *Laryngoscope* 2023; 133:344-349.
5. Kage H, Shinozaki-Ushiku A, Ishigaki K, Sato Y, Tanabe M, Tanaka S, Tanikawa M, Watanabe K, Kato S, Akagi K, Uchino K, Mitani K, Takahashi S, Miura Y, Ikeda S, Kojima Y, Watanabe K, Mochizuki H, Yamaguchi H, Kawazoe Y, Kashiwabara K, Kohsaka S, Tatsuno K, Ushiku T,

- Ohe K, Yatomi Y, Seto Y, Aburatani H, Mano H, Miyagawa K, Oda K. Clinical utility of Todai OncoPanel in the setting of approved comprehensive cancer genomic profiling tests in Japan. *Cancer Sci* (Online ahead of print)
6. Awano N, Urushiyama H, Yamana H, Yokoyama A, Ando T, Izumo T, Inomata M, Ito Y, Jo T. Validity of diagnoses of respiratory diseases recorded in a Japanese administrative database. *Respir Investig*. 2023 May;61(3):314-320.
 7. Horie M, Tanaka H, Suzuki M, Sato Y, Takata S, Takai E, Miyashita N, Saito A, Nakatani Y, Yachida S. An integrative epigenomic approach identifies ELF3 as an oncogenic regulator in ASCL1-positive neuroendocrine carcinoma. *Cancer Sci*. 2023 Jun;114(6):2596-2608.
 8. Mikami Y, Grubb BR, Rogers TD, Dang H, Asakura T, Kota P, Gilmore RC, Okuda K, Morton LC, Sun L, Chen G, Wykoff JA, Ehre C, Vilar J, Heusden C, Alessandra LB, Gentzsch M, Button B, Stutts MJ, Randell SH, O'Neal WK, Boucher RC. Chronic airway epithelial hypoxia exacerbates injury in muco-obstructive lung disease through mucus hyperconcentration, *Sci Transl Med*. 2023 Jun;15(699):eabo7728.
 9. Tamiya H, Mitani A, Abe T, Nagase Y, Isago H, Saito M, Yokoyama A, Ishimori T, Jo T, Tanaka G, Suzuki H, Nagase T. Practices of Inhaler Instruction to Patients with Obstructive Lung Diseases in Community Pharmacies: A Questionnaire Survey 医療薬学 (Japanese Journal of Pharmaceutical Health Care and Sciences) Vol. 49, No. 06, 2023
 10. Kage H, Oda K, Muto M, Tsuchihara K, Okita N, Okuma Y, Kikuchi J, Shirota H, Hayashi H, Kokuryo T, Sakai D, Hirasawa A, Kubo M, Kenmotsu H, Akiyama N, Shinozaki-Ushiku A, Tanabe M, Ushiku T, Miyagawa K, Seto Y. Human resources for administrative work to carry out a comprehensive genomic profiling test in Japan. *Cancer Sci* 2023;114:3041-3049
 11. Matsubara J, Mukai K, Kondo T, Yoshioka M, Kage H, Oda K, Kudo R, Ikeda S, Ebi H, Muro K, Hayashi R, Tokudome N, Yamamoto N, Muto M. First-Line Genomic Profiling in Previously Untreated Advanced Solid Tumors for Identification of Targeted Therapy Opportunities. *JAMA Netw Open*. 2023;6:e2323336
 12. Jo T, Shigemi D, Konishi T, Yamana H, Michihata N, Kumazawa R, Yokoyama A, Urushiyama H, Matsui H, Fushimi K, Nagase T, Yasunaga H. Antiemetic Effect of Rikkunshito, a Japanese Kampo Herbal Medicine, on Cisplatin-induced Nausea and Vomiting: A Nationwide Database Study in Japan. *Intern Med*. 2024 Apr 1;63(7):919-927. doi: 10.2169/internalmedicine.1946-23. Epub 2023 Jul 26.
 13. Fujita K, Arai R, Shoji S, Saito R, Nomura M, Hotta T, Asahina H, Kawakami M, Nakachi I, Hasegawa Y, Okafuji K, Suzuki A, Miyanaga A, Sunaga N, Nagashima H, Ikeda N, Watanabe S, Nagai Y, Furuta M, Kage H, Arai D, Fukuhara T, Nakayama M, Morita S, Kobayashi K, Hagiwara K. Detection of multiple druggable mutations of lung cancer from cytology specimens by MINtS: An advanced medicine A trial. *Cancer Sci* 2023; 114:3342-3351
 14. Kobayashi K, Saito Y, Kage H, Fukuoka O, Yamamura K, Mukai T, Oda K, Yamasoba T. CDK12 alterations and ARID1A mutations are predictors of poor prognosis and therapeutic targets in high-grade salivary gland carcinoma: analysis of the National Genomic Profiling Database. *Jpn J Clin Oncol*. 2023;53(9):798-807.
 15. Awano N, Jo T, Izumo T, Inomata M, Ito Y, Hashimoto Y, Matsui H, Fushimi K, Urushiyama H, Nagase T, Yasunaga H. Hospital volume and outcomes following bronchoscopy in patients with interstitial lung disease: A retrospective observational study using a national inpatient database in Japan. *Respir Investig*. 2023 Nov; 61(6):720-728. doi: 10.1016/j.resinv.2023.07.005. Epub 2023 Sep 13.
 16. Tamiya H, Mitani A, Abe M, Nagase T. Putative Bidirectionality of Chronic Obstructive Pulmonary Disease and Periodontal Disease: A Review of the Literature. *J Clin Med*. 2023; 12(18):5935
 17. Yoshida Y, Nishiyama A, Suameitria Dewi DNS, Yamazaki T, Yokoyama A, Kobayashi D, Kondo H, Ozeki Y, Matsumoto S. Limited proteolysis of mycobacterial DNA-binding protein 1 with an extended, lysine-rich, intrinsically disordered

- region to unveil posttranslational modifications. *Biochem Biophys Res Commun*. 2023 Nov 12;681:111-119. doi: 10.1016/j.bbrc.2023.09.028. Epub 2023 Sep 20. PMID: 37774568.
18. Fujii K, Fukuda K, Kawakami M, Mitani A, Tanaka G, Kage H. Lung Adenocarcinoma Size Decrease after SARS-CoV-2 Vaccination during Long-Term Pembrolizumab Treatment: A Case Report. *Case Rep Oncol*. 2023;16:907-911
 19. Nakai T, Watanabe T, Kaimi Y, Shiomi K, Ando K, Miyamoto A, Ogawa K, Matsumoto Y, Sawa K, Sato K, Asai K, Matsumoto Y, Mikami Y, Ohsawa M, Kawaguchi T, Diagnostic Utility and Safety of Non-Intubated Cryobiopsy Technique Using a Novel Ultrathin Cryoprobe in Addition to Conventional Biopsy Techniques for Peripheral Pulmonary Lesions, *Respiration*. 2023;102(7):503-514.
 20. Kato H, Kimura S, Taguchi M, Sunouchi T, Hoshino Y, Hidaka N, Edvige Foligno N, Koga M, Manaka K, Tamiya H, Kawakami M, Kage H, Yasunaga Y, Nangaku M, Makita N, Ito N. FGF23-related hypophosphatemia in a patient with small cell lung cancer: a case report and literature review. *Endocr J*. 2023;70:1005-1013
 21. Awano N, Jo T, Izumo T, Inomata M, Ito Y, Morita K, Matsui H, Fushimi K, Urushiyama H, Nagase T, Yasunaga H. Polymyxin B-immobilised fibre column treatment for acute exacerbation of idiopathic pulmonary fibrosis patients with mechanical ventilation: a nationwide observational study. *J Intensive Care*. 2023 Oct 11;11(1):45. doi: 10.1186/s40560-023-00693-0.
 22. Tamiya H, Abe M, Nagase T, Mitani A. The Link between Periodontal Disease and Asthma: How Do These Two Diseases Affect Each Other? *J Clin Med*. 2023;12(21):6747
 23. Kobayashi H, Zhang L, Okajima K, Ishibashi Y, Hirai T, Tsuda Y, Ikegami M, Kage H, Shinozaki-Ushiku A, Oda K, Tanaka S. BRAF mutations and concurrent alterations in patients with soft tissue sarcoma. *Genes Chromosomes Cancer* 2023;62:648-654
 24. Kobayashi K, Saito Y, Kamogashira T, Kage H, Fukuoka O, Yamamura K, Mukai T, Oda K, Yamasoba T. Survival analysis of high-grade salivary gland carcinoma adjusted for length bias due to delay in comprehensive genomic profiling. *Jpn J Clin Oncol*. 2023;53:1092-1093
 25. Yokoyama A, Jo T, Sakamoto Y, Urushiyama H, Tamiya H, Tanaka G, Kumazawa R, Matsui H, Fushimi K, Yasunaga H, Nagase T. Effectiveness and safety of the co-administration of Yokukan-San (Japanese herbal medicine) with antipsychotics in hospitalized older patients with pneumonia. *Geriatr Gerontol Int*. 2023 Nov;23(11):849-854. doi: 10.1111/ggi.14696. Epub 2023 Oct 7. PMID: 37804182.
 26. Konkimalla A, Konishi S, Macadlo L, Kobayashi Y, Farino ZJ, Miyashita N, El Haddad L, Morowitz J, Barkauskas CE, Agarwal P, Souma T, ElMallah MK, Tata A, Tata PR. Transitional cell states sculpt tissue topology during lung regeneration. *Cell Stem Cell*. 2023 Nov 2;30(11):1486-1502.e9.
 27. Ohara K, Miyawaki S, Nakatomi H, Okano A, Teranishi Y, Shinya Y, Ishigami D, Hongo H, Takayanagi S, Tanaka S, Shinozaki-Ushiku A, Kohsaka S, Kage H, Oda K, Miyagawa K, Aburatani H, Mano H, Tatsuno K, Saito N. Case report and literature review: exploration of molecular therapeutic targets in recurrent malignant meningioma through comprehensive genetic analysis with Todai OncoPanel. *Front Neurol*. 2023;14:1270046
 28. Tamiya H, Mitani A, Abe T, Nagase Y, Suzuki H, Jo T, Tanaka G, Nagase T. Association between Inhalation Instruction Method in Community Pharmacies and Inhaler Device Handling Error in Patients with Obstructive Lung Disease: An Evaluation of the Impact of Practical Demonstration by Pharmacists. *Biol Pharm Bull*. 2022;45(12):1764
 29. Saito Y, Kage H, Kobayashi K, Yoshida M, Fukuoka O, Yamamura K, Mukai T, Oda K, Yamasoba. TERT promoter mutation positive oral cavity carcinomas, a clinically and genetically distinct subgroup of head and neck squamous cell carcinomas. *Head Neck*. 2023;45:3107-3118
 30. Xi Q, Kage H, Ogawa M, Matsunaga A, Nishijima A, Sone K, Kawana K, Oda K. Genomic Landscape of Endometrial, Ovarian,

and Cervical Cancers in Japan from the Database
in the Center for Cancer Genomics and Advanced
Therapeutics. *Cancers (Basel)*. 2023;16:136

Department of Gastroenterology

Professor

Mitsuhiro Fujishiro, M.D., Ph.D.,

Ryosuke Tateishi, M.D., Ph.D.

Lecturer

Yoku Hayakawa, M.D., Ph.D.

Research Associate

Yotaro Kudo, M.D., Ph.D.,

Naminatsu Takahara, M.D., Ph.D.,

Ryota Takahashi, M.D., Ph.D.,

Tsuyoshi Hamada, M.D., Ph.D.,

Nobumi Suzuki, M.D., Ph.D.,

Tomotaka Saito, M.D., Ph.D.,

Tatsuya Sato, M.D., Ph.D.,

Ken Kurokawa, M.D., Ph.D.,

Kensaku Noguchi, M.D., Ph.D.,

Chihiro Takeuchi, M.D., Ph.D.,

Keisuke Yamamoto, M.D., Ph.D.

Koji Miyabayashi, M.D., Ph.D.,

Tatsuya Minami, M.D., Ph.D.,

Takahiro Kishikawa, M.D., Ph.D.,

Takuma Nakatsuka, M.D., Ph.D.,

Sozabuto Ihara, M.D., Ph.D.,

Tomoharu Yamada, M.D., Ph.D.,

Tatsunori Suzuki, M.D., Ph.D.,

Hiroki Oyama, M.D., Ph.D.,

Yu Miyakawa, M.D., Ph.D.

Project Research Associate

Yuko Miura, M.D., Ph.D.

Homepage <http://gastro.m.u-tokyo.ac.jp/>

Introduction and Organization

The Department of Gastroenterology was established through a reorganization of the Graduate School of Medicine and that of the Division of Internal Medicine of The University of Tokyo Hospital in 1998. The department is responsible for clinical services, education, and research activities in the liver, pancreato-biliary, and gastrointestinal tract. It comprises a professor, an associate professor, a lecturer, 21 assistant professors, 3 fellows, 49 graduates, and other visiting researchers including students from abroad as of March 2024. Some others are under a temporary transfer inside and outside the country. The

North and South wings on the 11th floor of Ward A have provided core hospital rooms for the department. Laboratories of the department are scattered on each floor, mainly of Clinical Research Center.

Clinical activities

The Department of Gastroenterology owns 74 inpatient beds in charge. By using these beds, we saw total 24,411 inpatients with 2,656 new inpatients in an average hospital stay of 9.2 days in the fiscal year of 2023. Resident, junior and senior staff members bear the responsibility for the medical management of each inpatient in collaboration with subspecialty groups

concerned. We saw total 61,679 outpatients with 1,657 new outpatients (2.7%) in the fiscal year of 2023. Specialty and subspecialty clinical conferences are held on Monday evening.

The number of treatments for hepatocellular carcinoma, represented by percutaneous radiofrequency ablation, nearly 200 cases per year, is showing one of the greatest achievements in the field. Combination immunotherapy, including immune checkpoint inhibitors, has become the mainstay of treatment for advanced hepatocellular carcinoma, and our department is also introducing about 60 new cases per year. Due to recent advances in viral hepatitis treatment and the increase in the number of obese population, the focus of liver disease is shifting from viral hepatitis to fatty liver disease, including metabolic dysfunction-related fatty liver disease (previously known as non-alcoholic fatty liver disease). Drug development is also active in this field, and our department is conducting a number of clinical trials, and is leading clinical trials of cognitive behavioral therapy using smartphone apps. The non-invasive liver stiffness measurement method FibroScan, which we have been using for 20 years, can also measure the amount of liver fat, and is useful for screening for fatty liver.

We perform about 1,000 cases of endoscopic ultrasonography (EUS) and endoscopic retrograde cholangiopancreatography (ERCP), the standard endoscopic procedures for biliary and pancreatic diseases, annually. We have evaluated over 4,000 pancreatic cystic neoplasms, and also performed various endoscopic treatments such as endoscopic extraction of bile duct stones in over 1,500 cases and biliary drainage with metal stents for malignant biliary strictures in over 1,200 cases, too. We have contributed to development and reported clinical studies on endoscopic papillary balloon dilation (EPBD) and papillary large balloon dilation (EPLBD) for the treatment of bile duct stones, and covered metal stents for malignant as well as benign biliary strictures. Our expertise includes advanced endoscopic treatment for patients who are difficult to manage by standard treatment, such as ERCP using a balloon endoscope and transluminal drainage, EUS-guided stone extraction in cases with surgically altered anatomy, endotherapy for pancreatic stone and stricture. In cases with pancreatic and biliary tract cancer, we have

investigating new chemotherapeutic regimens and recently introduced preoperative chemotherapy for resectable pancreatic cancer. Comprehensive genome profiling is performed using tumor specimens collected by EUS-FNA to facilitate individualized treatment. The number of cases of intractable diseases such as primary sclerosing cholangitis and IgG4-related diseases, is one of the highest in Japan.

In the gastrointestinal field, ESD (endoscopic submucosal dissection) is performed as a curative endoscopic treatment for neoplasms in the esophagus, stomach, or colon (approximately 500 patients a year). Collaborative endoscopic surgery with other departments is actively performed: 1) ESD for superficial pharyngeal cancer is often performed in cooperation with the department of otorhinolaryngology; 2) ESD for duodenal epithelial tumor with the support of the Department of Gastrointestinal Surgery, 3) as for Non-exposed endoscopic wall-inversion surgery (NEWS), which was developed with the Department of Gastrointestinal Surgery, its clinical indication has been now expanded from the resection of GIST to the treatment of gastric cancer. In 2021, 'Endoscopic full-thickness resection for submucosal tumor' has been approved as a highly challenging novel medical technology with the support of the Department of Gastrointestinal Surgery. Our challenge to novel endoscopic procedures continues. Double-balloon endoscopy (DBE) and capsule endoscopy (CE) enabled the examination of whole small intestines (approximately 90 cases in 2023). Especially in inflammatory bowel disease (IBD) patients, we perform the examination using an optimal method including DBE, CE, and MR enterography. In severe IBD cases, we conduct the combination therapy of conventional immunosuppressive drugs and the latest biologics to increase QOL and achieve mucosal healing and prevention of relapse. About 400 metal stent placements for malignant gastrointestinal obstruction have been performed at our facility. All those interventions are performed by the members of our department, who are specially trained for each technique. In addition, for the management of inoperative malignancies, we effectively combine the interventional treatments with various chemotherapy regimens including immuno-checkpoint inhibitor. Aiming at personalized medicine based on genetic

information, we are also actively conducting cancer multi-gene panel testing.

On an outpatient basis, the number of performed gastroduodenal endoscopy, and colonoscopy is 11,000 patients and 6,000 patients per year, respectively. In the endoscopy examinations, we diagnose approximately 380 cases of esophageal cancer, 550 cases of gastric cancer, and 700 cases of colorectal tumor annually. We perform various basic studies using these resected tissues to feed the new finding back to actual clinical activities.

Teaching activities

The undergraduate medical students regularly take the clinical lectures of the staff in our department. Several courses of practical teaching are also provided for the students. Particularly, in the Clinical Clerkship program during the fifth grade, each student joins in the medical treatment of inward patients as a member of the clinical team in our hospital. At the end of the period, the students make a summary presentation of the patients and also outline the articles from the world's leading medical journals.

The residents of internal medicine participate in the training of our department for 1-4 months in the first year. They learn the knowledge of therapeutics and diagnostics in gastroenterology as well as general internal medicine. Our department deals with the training curriculum as a medical specialist of internal medicine. The residents in the course are supported to experience some diseases in the gastrointestinal field. The residents who major in gastroenterology as a subspecialty take the expert training of gastroenterology in the affiliated hospitals for several years.

The students of the Department of Gastroenterology in the Graduate School of Medicine perform a high standard of medical research in the basic or clinical field for four years.

Research activities

Both basic and clinical researchers are equally encouraged on the condition that the results may eventually contribute to the cure of gastroenterological disorders. The themes of our recent basic researches include the study on carcinogenesis in

gastroenterological neoplasms, mechanism of viral hepatitis infection, the pathogenesis of metabolic liver diseases, liver regeneration, liver fibrosis, pathogenesis of *Helicobacter pylori* infection, molecular characterization of gastrointestinal morphology, establishing new animal models, tracing cell differentiation, and stem cell biology for various diseases in our area. Using new concepts such as transparent organs, genomic and epigenomic profiling of clinical samples, microbiome, organoids, or liquid biopsy, we perform various experiments to translate the basic results into clinics eventually.

Various clinical activities are recorded in database and analyzed. Studies oriented toward evidence-based medicine are highly appreciated. Recent studies include multicenter study to investigate the impact of metabolic factors in hepatocarcinogenesis, AI-based prediction of liver carcinogenesis using digital pathology images of liver biopsies and studies using nationwide registry for liver diseases. We have also designed many clinical trials as follows; Effects of various drug treatments on advanced hepatocellular carcinoma, SNPs analyses for antiviral treatment for hepatitis C, new chemotherapeutic regimens for advanced pancreatic cancer or biliary tract cancer, balloon endoscope-assisted ERCP for surgically altered anatomy, the efficacy of polyglycolic acid sheets for artificial endoscopic ulcers, development of AI for assisted endoscopic diagnosis, and personalized salvage therapy of *Helicobacter* infection.

Our department always tries to show the newest and highest-level clinical activities, based on the various data of many patients, especially those suffering from malignant diseases. Furthermore, we aim to find the new aspects of diseases and create a new strategy against them, which is based on clinical, basic, and epidemiological studies in our area. And in collaboration with Faculty of engineering, we are actively promoting projects to advance new medical materials and therapeutic devices through medical-engineering collaboration.

Selected References

1. Fukagawa K, Takahashi Y, Yamamichi N, Kageyama-Yahara N, Sakaguchi Y, Obata M, Cho R, Sakuma N, Nagao S, Miura Y, Tamura N, Ohki

- D, Mizutani H, Yakabi S, Minatsuki C, Niimi K, Tsuji Y, Yamamichi M, Shigi N, Tomida S, Abe H, Ushiku T, Koike K, Fujishiro M. Transcriptome analysis reveals the essential role of NKX2-1/TTF-1 in gastric adenocarcinoma of fundic-gland type. *Gastric Cancer*. 2023;26:44-54.
2. Kato H, Tateishi K, Iwadate D, Yamamoto K, Fujiwara H, Nakatsuka T, Kudo Y, Hayakawa Y, Ijichi H, Otsuka M, Kishikawa T, Takahashi R, Miyabayashi K, Nakai Y, Hirata Y, Toyoda A, Morishita S, Fujishiro M. HNF1B-driven three-dimensional chromatin structure for molecular classification in pancreatic cancers. *Cancer Sci*. 2023;114:1672-168.
3. Sato M, Akamatsu M, Shima T, Ikegami T, Yanase M, Mikami S, Imamura J, Nakatsuka T, Tateishi R, Yamauchi N, Ushiku T, Okanoue T, Fujishiro M, Hida E, Koike K. Impact of a Novel Digital Therapeutics System on Nonalcoholic Steatohepatitis: The NASH App Clinical Trial. *Am J Gastroenterol*. 2022;118:1365-1372.
4. Hamada T, Oyama H, Nakai Y, Tange S, Arita J, Hakuta R, Ijichi H, Ishigaki K, Kanai S, Kawaguchi Y, Kogure H, Mizuno S, Saito K, Saito T, Sato T, Suzuki T, Takahara N, Tanaka M, Tateishi K, Ushiku T, Hasegawa K, Fujishiro M. Clinical Outcomes of Intraductal Papillary Mucinous Neoplasms With Dilatation of the Main Pancreatic Duct. *Clin Gastroenterol Hepatol*. 2023;21:1792-1801.
5. Nakatsuka T, Tateishi R, Sato M, Fujishiro M, Koike K. Agile scores are a good predictor of liver-related events in patients with NAFLD. *J Hepatol*. 2023;79:e126-e127.
6. Niikura R, Hayakawa Y, Nagata N, Miyoshi-Akiyama T, Miyabayashi K, Tsuboi M, Suzuki N, Hata M, Arai J, Kurokawa K, Abe S, Uekura C, Miyoshi K, Ihara S, Hirata Y, Yamada A, Fujiwara H, Ushiku T, Woods SL, Worthley DL, Hatakeyama M, Han YW, Wang TC, Kawai T, Fujishiro M. Non-*Helicobacter pylori* Gastric Microbiome Modulates Prooncogenic Responses and Is Associated With Gastric Cancer Risk. *Gastro Hep Adv*. 2023;2:684-700.
7. Seimiya T, Otsuka M, Fujishiro M. Overcoming T-cell exhaustion: New therapeutic targets in HCC immunotherapy. *Hepatology*. 2023;78:1009-1011.
8. Yamada T, Fujiwara N, Kubota N, Matsushita Y, Nakatsuka T, Kurosaki S, Minami T, Tateishi R, Ichida A, Arita J, Hasegawa K, Koike K, Fujishiro M, Nakagawa H. Lenvatinib recruits cytotoxic GZMK+CD8 T cells in hepatocellular carcinoma. *Hepatol Commun*. 2023;7:e0209.
9. Oyama H, Hamada T, Nakai Y, Tanaka M, Endo G, Hakuta R, Ishida K, Ishigaki K, Kanai S, Kurihara K, Saito T, Sato T, Suzuki T, Suzuki Y, Takaoka S, Tange S, Tokito Y, Takahara N, Ushiku T, Fujishiro M. Clinical trajectory of intraductal papillary mucinous neoplasms progressing to pancreatic carcinomas during long-term surveillance: a prospective series of 100 carcinoma cases. *J Gastroenterol*. 2023;58:1068-1080.
10. Saito K, Michihata N, Hamada T, Jo T, Matsui H, Fushimi K, Nakai Y, Yasunaga H, Fujishiro M. Gemcitabine plus nab-paclitaxel for pancreatic cancer and interstitial lung disease: A nationwide longitudinal study. *Cancer Sci*. 2023;114:3996-4005.
11. Hamada T, Oyama H, Nakai Y, Fujishiro M. Risk Stratification Based on Cyst Size and Its Stability for Low-Risk Intraductal Papillary Mucinous Neoplasms: Which Size Matters? *Am J Gastroenterol*. 2023;118:1705-1706.
12. Soeda K, Sasako T, Enooku K, Kubota N, Kobayashi N, Ikushima YM, Awazawa M, Bouchi R, Toda G, Yamada T, Nakatsuka T, Tateishi R, Kakiuchi M, Yamamoto S, Tatsuno K, Atarashi K, Suda W, Honda K, Aburatani H, Yamauchi T, Fujishiro M, Noda T, Koike K, Kadowaki T, Ueki K. Gut insulin action protects from hepatocarcinogenesis in diabetic mice comorbid with nonalcoholic steatohepatitis. *Nat Commun*. 2023;14:6584.
13. Miura Y, Tsuji Y, Yoshio T, Hatta W, Yabuuchi Y, Hoteya S, Kikuchi D, Tsuji S, Nagami Y, Hikichi T, Kobayashi M, Morita Y, Sumiyoshi T, Iguchi M, Tomida H, Inoue T, Mikami T, Hasatani K, Nishikawa J, Matsumura T, Nebiki H, Nakamatsu D, Ohnita K, Suzuki H, Ueyama H, Hayashi Y, Sugimoto M, Yamaguchi S, Michida T, Yada T, Asahina Y, Narasaka T, Kuribayashi S, Kiyotoki S, Mabe K, Masamune A, Fujishiro M. Association

- between perioperative management of antiplatelet agents and risk of post-endoscopic submucosal dissection bleeding in early gastric cancer: analysis of a nationwide multicenter study. *Gastrointest Endosc.* 2023;97:889-897.
14. Arai J, Niikura R, Hayakawa Y, Suzuki N, Honda T, Okamura T, Hasatani K, Yoshida N, Nishida T, Sumiyoshi T, Kiyotoki S, Ikeya T, Arai M, Boku N, Fujishiro M. Association of probiotic use with nivolumab effectiveness against various cancers: A multicenter retrospective cohort study. *Cancer Med.* 2023;12:16876-16880.
 15. Fukuda R, Hakuta R, Nakai Y, Hamada T, Takaoka S, Tokito Y, Suzuki Y, Oyama H, Kanai S, Noguchi K, Suzuki T, Ishigaki K, Saito K, Saito T, Takahara N, Mizuno S, Ito Y, Kogure H, Fujishiro M. Development and external validation of a nomogram for prediction of post-endoscopic retrograde cholangiopancreatography pancreatitis. *Pancreatology.* 2023;23:789-796.
 16. Kado A, Tsutsumi T, Yotsuyanagi H, Ikeuchi K, Okushin K, Moriya K, Koike K, Fujishiro M. Noninvasive approach to indicate risk factors of nonalcoholic steatohepatitis overlapping autoimmune hepatitis based on peripheral lymphocyte pattern. *J Gastroenterol.* 2023;58:1237-1251.
 17. Okushin K, Yamana H, Tateishi R, Sato M, Tsutsumi T, Matsui H, Fushimi K, Yasunaga H, Koike K, Fujishiro M. Treatment and outcome of hepatorenal syndrome in Japan: a retrospective cohort study using a national inpatient database. *BMC Gastroenterol.* 2023;23:218.
 18. Sakaguchi Y, Tsuji Y, Sato J, Kubota D, Obata M, Cho R, Nagao S, Miura Y, Ohki D, Mizutani H, Yakabi S, Kakushima N, Niimi K, Fujishiro M. Repeated steroid injection and polyglycolic acid shielding for prevention of refractory esophageal stricture. *Surg Endosc.* 2023;37:6267-6277.
 19. Sakaguchi Y, Saito Y, Ando M, Yoshida M, Fukuoka O, Kobayashi K, Kubota D, Ohki D, Mizutani H, Niimi K, Tsuji Y, Fujishiro M, Yamasoba T. Risk factors for incomplete resection with pharyngeal endoscopic submucosal dissection and long-term prognosis after resection. *Surg Endosc.* 2023;37:3593-3601.
 20. Aoki T, Yamada A, Kobayashi K, Yamauchi A, Omori J, Ikeya T, Aoyama T, Tominaga N, Sato Y, Kishino T, Ishii N, Sawada T, Murata M, Takao A, Mizukami K, Kinjo K, Fujimori S, Uotani T, Fujita M, Sato H, Suzuki S, Narasaka T, Hayasaka J, Funabiki T, Kinjo Y, Mizuki A, Fujishiro M, Kaise M, Nagata N; Collaborators. Development and validation of a novel model for predicting stigmata of recent hemorrhage in acute lower gastrointestinal bleeding: Multicenter nationwide study. *Dig Endosc.* 2023;35:777-789.

Internal Medicine

2. Medicine II

Department of Nephrology and Endocrinology

Professor

Masaomi Nangaku, M.D., Ph.D.

Associate professor

Noriko Makita, M.D., Ph.D.,

Hiroshi Nishi, M.D., Ph.D.

Lecturer

Motonobu Nakamura, M.D., Ph.D.,

Yoshifumi Hamasaki, M.D., Ph.D.

Hospital Lecturer

Imari Mimura, M.D., Ph.D.

Associate

Junichiro Sato, M.D., Ph.D.,

Yoichiro Ikeda, M.D., Ph.D.,

Maki Takeuchi, M.D., Ph.D.,

Shinji Tanaka, M.D., Ph.D.,

Toshiko Kobori, M.D., Ph.D.,

Yosuke Hirakawa, M.D., Ph.D.,

Mai Sugahara, M.D., Ph.D.,

Kotaro Doi, M.D., Ph.D.,

Yu Kurata, M.D., Ph.D.,

Fumiaki Tanemoto, M.D., Ph.D.

Official website: <http://www.todai-jinnai.com>

Overview of the organization

The Department of Nephrology and Endocrinology consists of approximately 90 members, including 1 professor, 2 associate professors, 2 lecturers, 1 specially appointed lecturer, 10 assistant professors, 2 medical staff, and graduate students. In addition, the Department of International Medicine, the Department

of Intensive Care, the Department of Infection Control, the Office of Research Ethics Support, and the Department of Computer Diagnostic Imaging and Preventive Medicine have produced staff. The medical research and educational activities of our department are carried out in close cooperation with specialized groups in each of the closely related fields of nephrology, endocrinology, and hypertension. In

addition, in collaboration with the Department of Hemodialysis and Apheresis, we provide blood purification therapy such as hemodialysis and peritoneal dialysis for renal failure, and kidney transplantation in collaboration with the Department of Urology.

Clinical activities

In the outpatient clinic, outpatients specializing in kidneys, endocrinology, and hypertension are in charge of new patients and returning patients every day. The outpatient department of general internal medicine is also shared. In addition, we are actively working on the introduction and maintenance of peritoneal dialysis patients and collaboration with other hospitals in combination with hemodialysis.

Hospitalizations are mainly provided to the north of the 14th floor of Inpatient Building A, and about 20 inpatients are treated at any given time. The breakdown of hospitalized patients ranges from glomerulonephritis, nephrosis, hypertension (including endocrine), conservative renal failure, diabetic nephropathy, dialysis induction patients, acute renal failure, diencephalic pituitary disease, adrenal gland disease, thyroid disease, parathyroid disease, and bone mineral metabolism disease. Faculty rounds are held every Tuesday at 9 a.m., and new patient presentations and weekly presentations are held prior to the rounds. In addition, patients with kidney and endocrine diseases who are hospitalized in other departments are actively involved in the treatment of patients with renal and endocrine diseases by forming a consulting team.

As for the medical care system, a team of residents, ward supervisors (in charge), specialist supervisors (attending physicians), and supervising physicians are formed, and the supervising physician who is responsible for each resident is determined, and care is taken to ensure that there are no omissions. The treatment policy is checked through renal and endocrine conferences, and finally in the presentation before rounds. Medical procedures include renal biopsy, various endocrine stress tests, ultrasound diagnosis, and preparation for hemodialysis. A renal biopsy conference is held once a month to discuss with doctors from the Department of Pathology,

Allergy and Rheumatology, and Pediatrics as a histopathological review group for kidney biopsy cases, and a renal transplant conference is held once a month to discuss kidney transplant cases jointly with the Department of Urology. In addition, we fully cooperate with the operation of the Department of Blood Purification Therapy, and in addition to providing chronic hemodialysis therapy for all inpatients at the University of Tokyo Hospital who are hospitalized in other departments for other diseases, we also provide hemodialysis therapy for acute kidney injury associated with heart and vascular surgery. In addition, we also perform plasmapheresis before and after liver transplantation in cooperation with transplant surgery, as well as adsorption therapy for other diseases.

In the diagnosis of endocrine diseases, we are promoting vein sampling and various diagnostic imaging in cooperation with the Department of Radiology. In the treatment of endocrine diseases, radioactive iodine treatment for Graves' disease is performed in collaboration with the Department of Radiology. In addition, we provide treatment for diencephalic pituitary disease, adrenal gland disease, thyroid crisis, thyroid tumor, parathyroid tumor, etc., in close cooperation with neurosurgery, urology, and breast endocrine surgery.

Education activities

As a pre-graduate education, clinical clerkship is divided between diagnostics, internal medicine lectures, internal medicine clinical lectures, and clinical clerkship. The lectures are nephrology and endocrinology. In the clinical clerkship, we provide a more in-depth explanation of various cases in each field from a specialized standpoint, and in particular, we provide access to the actual treatment of hemodialysis as a treatment for end-stage renal failure. In addition, we are promoting the Metabolism Research Course, a clinical researcher training program, jointly with the departments of diabetes, metabolism, cardiology, and geriatrics.

For post-graduate education, residents are instructed in the ward throughout the year (1 to 2 months in the first term). Each resident is assigned a team of junior medical staff and assistant professors

specializing in nephrology and endocrinology, and is responsible for providing guidance. Every Thursday, we hold a conference in the blood purification therapy room not only for inpatients in the Department of Nephrology and Endocrinology, but also for other internal medicines such as cardiology and gastroenterology, as well as dialysis patients and patients undergoing blood purification therapy in other departments, including surgery (especially cardiac surgery and vascular surgery).

Monthly case review meetings play an important role in the education of residents and junior medical officers.

Research activities

It is broadly divided into kidney and endocrine, but there is also an overlap in hypertension.

(kidney)

1. Elucidation of the progression mechanism of chronic kidney disease and development of treatment methods (from the viewpoints of hypoxia, oxidative stress, endoplasmic reticulum stress, carbonyl stress, epigenetics, etc.)
2. Research on epigenetic abnormalities in progressive kidney injury
3. Research on atypical hemolytic uremic syndrome
4. Study of the mechanism of urine protein and renal protein metabolism
5. Examination of renal biopsy tissue findings, incidence and long-term prognosis
6. Significance of renal proximal tubular transport in fluid regulation and hypertension development
7. Physiological significance of the Na-HCO₃ cotransporter NBCe1

(Endocrine)

1. Analysis of the molecular mechanisms of G-protein-coupled signal transduction and disease, and design of new drugs and control methods
2. Examination of the etiology and treatment of mineral and bone metabolism disorders
3. Clinical research targeting endocrine diseases

After the case review meeting, a research conference is held, where all members of the department, from professors to graduate students,

present their research, invite external lecturers to give lectures, and rehearse conferences.

Department of Hemodialysis and Apheresis

This department was established and put into operation in Heisei 12 as one of the central medical facilities of this hospital, and is one of the relatively new departments of the University of Tokyo Hospital. In the past, each department had dealt with renal failure individually, but such a response was inefficient in terms of equipment and human resources, so it was established with the aim of coordinating related departments. In December 2018, we started a new medical treatment in the Central Clinic Building 2, and the current blood purification therapy room has 12 beds, including one private room that can control pressure. In the process of developing a system that fully responds to the peculiarities of our hospital and comprehensively implementing not only hemodialysis but also purification therapy such as plasmapheresis therapy and immunoadsorption therapy, we secure instrumental information, biological information, and accounting information as electronic information, and systematically implement our in-hospital system. It is now possible to link information to HIS. At the same time, by converting the information on ICU dialysis, continuous dialysis, plasmapheresis, etc., which are the operations of our department, to the cloud, it is possible to monitor in real time from anywhere in the hospital. By unifying the equipment, such a high level of safety, transparency, and educational nature is ensured.

(1) Education

The pre-graduate education includes systematic lectures on M2, which covers understanding the pathophysiology of renal failure, the natural history and treatment of renal disease, and the pathophysiology and clinical research of diabetic nephropathy, which has been rapidly increasing as the number one disease in dialysis patients in recent years. BSL is not performed by the Department of Blood Purification Therapy, but the content related to the treatment of renal failure in education in the Department of Nephrology and Endocrinology is shared. In collaboration with the Emergency

Department and Intensive Care Department, we are promoting the Critical care nephrology course in the clinical researcher training program. In the postgraduate training education, mainly for those who wish to participate in the second semester training, we will focus on the basic concept of dialysis treatment, continuous hemofiltration therapy, plasmapheresis, and continuous hemofiltration therapy that is performed on a daily basis. We taught how to grasp the pathology and determine the prescription of special treatments such as GCAP, and these manuals were divided into two parts: the Apheresis Therapy Pocket Manual (2nd Edition) and the CRRT Pocket Manual. The Apheresis Therapy Pocket Manual (2nd edition) has been translated into English and Chinese in addition to Japanese, and has been well received.

(2) Medical treatment

We provide a variety of blood purification therapies such as induction of dialysis for end-stage renal failure, inpatient dialysis of maintenance hemodialysis patients admitted to each department for examination and treatment, continuous hemofiltration dialysis and hemodialysis for ICU acute renal failure, plasmapheresis before and after neurological diseases, autoimmune diseases, liver transplantation, immunoadsorption therapy, and leukocyte ablation therapy. With the system modification, online HDF and I-HDF can also be implemented from 2019. The introduction and maintenance of peritoneal dialysis is also actively carried out in cooperation with the Department of Nephrology and Endocrinology. Internationally, AKIN (Acute Kidney Injury Network) and ADQI (Acute Acute Dialysis Quality Initiative).

(3) Research

Taking advantage of the peculiarities of our hospital, we have developed a non-invasive hemoglobin meter using the pulse photometry method and are using it for international support. We are conducting research to clarify the relationship between factors in the introduction of renal replacement therapy and long-term prognosis. In basic research, we are conducting elucidating the pathophysiology of acute renal failure, research on regenerative medicine using a model of acute renal failure, establishment of a mouse progressive renal

injury model, molecular biology and physiological research on renal disease biomarkers and pathophysiology, epidemiological research, and international cooperation on urine biomarkers. Using the data of patients who have undergone dialysis at our hospital, we are investigating the relationship between various factors during the introduction of renal replacement therapy and long-term prognosis. For peritoneal dialysis, we are analyzing factors related to patient prognosis, the occurrence of infectious diseases, which are major complications, and the factors that affect the treatment effect.

Publications

1. Arai M, Ochi H, Sunamura S, Ito N, Nangaku M, Takeda S, et al. A Novel Long Noncoding RNA in Osteocytes Regulates Bone Formation through the Wnt/ β -Catenin Signaling Pathway. *Int J Mol Sci.* 2023; 24(17).
2. Cherney DZI, de Zeeuw D, Heerspink HJL, Cardona J, Desch M, Wenz A, et al. Safety, tolerability, pharmacodynamics and pharmacokinetics of the soluble guanylyl cyclase activator BI 685509 in patients with diabetic kidney disease: A randomized trial. *Diabetes Obes Metab.* 2023; 25(8):2218-26.
3. Doi K, Kimura H, Kim SH, Kaneda S, Wada T, Tanaka T, et al. Enhanced podocyte differentiation and changing drug toxicity sensitivity through pressure-controlled mechanical filtration stress on a glomerulus-on-a-chip. *Lab Chip.* 2023; 23(3):437-50.
4. Green JB, Mottl AK, Bakris G, Heerspink HJL, Mann JFE, McGill JB, et al. Design of the COMbination effect of FInerenone and Empagliflozin in participants with chronic kidney disease and type 2 diabetes using a UACR Endpoint study (CONFIDENCE). *Nephrol Dial Transplant.* 2023; 38(4):894-903.
5. Hamano T, Imaizumi T, Hasegawa T, Fujii N, Komaba H, Ando M, et al. Biopsy-proven CKD etiology and outcomes: the Chronic Kidney Disease Japan Cohort (CKD-JAC) study. *Nephrol Dial Transplant.* 2023; 38(2):384-95.
6. Hasegawa T, Imaizumi T, Hamano T, Murotani K,

- Fujii N, Komaba H, et al. Association between serum iron markers, iron supplementation and cardiovascular morbidity in pre-dialysis chronic kidney disease. *Nephrol Dial Transplant*. 2023; 38(12):2713-22.
7. Hashiba T, Sugahara M, Ota Y, Kaseda K, Kashiwagi Y, Nakamura M, et al. Paralytic Ileus during Treatment of Pulmonary and Renal Tuberculosis in a Non-Human Immunodeficiency Virus Patient: An Unusual Presentation of Tuberculosis-immune Reconstitution Inflammatory Syndrome. *Intern Med*. 2023; 62(17):2559-64.
 8. Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ, Emberson JR, et al. Empagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med*. 2023; 388(2):117-27.
 9. Hidaka N, Inoue K, Kato H, Hoshino Y, Koga M, Kinoshita Y, et al. FGF-23, Left Ventricular Hypertrophy, and Mortality in Patients With CKD: A Revisit With Mediation Analysis. *JACC Adv*. 2024; 3(1):100747.
 10. Hidaka N, Murata H, Tachikawa K, Osaki K, Sekiyama T, Kinoshita Y, et al. The Effect of Asfotase Alfa on Plasma and Urine Pyrophosphate Levels and Pseudofractures in a Patient With Adult-Onset Hypophosphatasia. *JBMR Plus*. 2023; 7(12):e10842.
 11. Hoshino Y, Manaka K, Sato J, Asatsuma Y, Horikoshi H, Takeuchi M, et al. Recurrent bilateral adrenal infarction with myelodysplastic/myeloproliferative neoplasm-unclassifiable (MDS/MPN-U): a case report. *BMC Endocr Disord*. 2023; 23(1):128.
 12. Ikejiri K, Suzuki T, Muto S, Takama H, Yamawaki K, Miyazawa T, et al. Effects of NRF2 polymorphisms on safety and efficacy of bardoxolone methyl: subanalysis of TSUBAKI study. *Clin Exp Nephrol*. 2024; 28(3):225-34.
 13. Ishide T, Nishi H, Miyano S, Hirakawa Y, Honda K, Abe H, et al. Kidney Podocyte Zebra Bodies after Lung Transplantation for Lymphangioleiomyomatosis. *Intern Med*. 2023; 62(13):1965-70.
 14. Itano S, Kanda E, Nagasu H, Nangaku M, Kashihara N. eGFR slope as a surrogate endpoint for clinical study in early stage of chronic kidney disease: from The Japan Chronic Kidney Disease Database. *Clin Exp Nephrol*. 2023; 27(10):847-56.
 15. Kaneko H, Yano Y, Okada A, Itoh H, Suzuki Y, Yokota I, et al. Age-Dependent Association Between Modifiable Risk Factors and Incident Cardiovascular Disease. *J Am Heart Assoc*. 2023; 12(2):e027684.
 16. Kato H, Kimura S, Taguchi M, Sunouchi T, Hoshino Y, Hidaka N, et al. FGF23-related hypophosphatemia in a patient with small cell lung cancer: a case report and literature review. *Endocr J*. 2023; 70(10):1005-13.

Department of Diabetes and Metabolic Diseases

Professor

Toshimasa Yamauchi, M.D., Ph.D.

Associate Professor

Nobuhiro Shojima, M.D., Ph.D.

Lecturer

Masaki Igarashi, M.D., Ph.D.

Hospital Lecturer

Tomohisa Aoyama, M.D., Ph.D.,

Yoshitaka Sakurai, M.D., Ph.D.

Assistant Professor

Mikio Takanashi, M.D., Ph.D.,

Gotaro Toda, M.D., Ph.D.

Masakazu Aihara, M.D., Ph.D.,

Masaomi Miura, M.D., Ph.D.

Sara Odawara, M.D. Ph.D.,

Ken Suzuki, M.D., Ph.D.

Official website <https://dm.m.u-tokyo.ac.jp/>

Introduction and Organization

In 1998 the Department of Internal Medicine at the University of Tokyo was reorganized to the more functional units based on clinical specialties. The physicians specialized in diabetes and metabolic diseases from “The Third Department of Internal Medicine” were unified to the Department of Metabolic Diseases. The Department of Diabetes and Metabolic Diseases is one of the major divisions in the Department of Internal Medicine at the University of Tokyo, and covers diabetes mellitus and metabolic diseases including obesity disease and dyslipidemia.

Under the supervision and direction of the previous professors Dr. Satoshi Kimura (1998-2003), Dr. Toshiro Fujita (2003), Takashi Kadowaki (2003-2018) and current professor Dr. Toshimasa Yamauchi (2018-present), we have been providing a wide-ranged clinical, teaching and research activities. Currently, we hold beds mainly on the 12th floor of the North

Wing Ward A of the University of Tokyo Hospital. Besides the staffs listed above, our division holds faculties in branches, for example, Department of Clinical Nutrition Therapy (Associate Professor: Dr. Naoto Kubota), Laboratory for Advanced Research on Pathophysiology of Metabolic Diseases (Project Associate Professor: Dr. Miki Okada-Iwabu), Department of Healthcare Information Management (Associate Professor: Dr. Kayo Waki, Project Assistant Professor: Dr. Kana Miyake), Department of Clinical Laboratory (Professor: Dr. Makoto Kurano), Center for international Preventive Medicine (Hospital Lecturer: Dr. Yoko Iizuka), Division for Health Service Promotion, The University of Tokyo (Assistant Professor: Dr. Sachiko Okazaki) and Center for Epidemiology and Preventive Medicine (Project Assistant Professor: Dr. Yukari Masuda). With all these staffs, we actively instruct and teach the residents and medical school students. There are 24 students of Graduate School in our division. With all

these 54 members, we enthusiastically work on the research activities, which lead to the outstanding contributions in the field of metabolism.

Clinical activities

Based on the update clinical evidences and with the experienced skills, we provide patient-centered medical services in the highest quality. We have outpatient clinics from Monday through Friday, and have been following approximately 187 new patients this year (total 32,418 patients per year). On the inpatient ward, we not only take care of around 13 patients in our division as mentioned above, but also provide a sophisticated management to all patients suffering from metabolic diseases, especially diabetes mellitus. Diabetes mellitus, metabolic syndrome, dyslipidemia and obesity disease are becoming more prevalent in Japan, and lead to complications including nephropathy, retinopathy, neuropathy and cardiovascular diseases. Thus, in collaboration with other departments, we optimize the treatment of each patient.

We provide the educational classes to the patients twice a week in the inpatient ward. In addition, in collaboration with ancillary staffs of our hospital, we provide patients well-reasoned instructions regarding nutritional management, exercise therapy and medical therapy.

The weekly official activity of our department is a case conference by the Professor and the staffs on Monday. We also hold a weekly case conference by the consultation group staffs.

Teaching activities

As for medical student education, our department takes a part in systemic lectures for the 4th year medical students, bed-side learning and clinical clerkship for the 5th year medical students, and clinical lectures for the 6th year medical students.

In systemic lectures, comprehensive presentation for the understanding of basic knowledge about the concept, pathogenesis, diagnosis and treatment of common metabolic diseases is performed.

In clinical lectures, we present clinical cases of important diseases such as diabetes mellitus, and try to discuss with the students several points for

planning the diagnosis and treatment in collaboration with the faculties of the Departments of Nephrology, Cardiology, Ophthalmology, Geriatric Medicine, and Stress Sciences and Psychosomatic Medicine.

During the period of clinical clerkship, the students have opportunities to experience the daily clinical care with junior and senior residents as well as with the faculty members. Each student can learn how to do history taking, perform physical examinations and make the actual plans for the diagnosis and treatment. In addition, we arrange the program so that the students can experience the clinical practice and learn the disease itself more profoundly. One faculty and one senior-resident always instruct one student. Especially, Diabetes Clinical Seminar and oral examination that lead to profound understandings of the metabolic diseases are regularly provided by the Professor.

As for the post-graduate education, attending doctor (staff) and senior resident instruct the junior residents. We also support junior and senior residents to present case reports at several meetings of The Japanese Society of Internal Medicine and the Japan Diabetes Society.

Research activities

There are several laboratories in our departments; collaborating with each other or with other departments, we focus on the molecular mechanisms of the metabolic diseases and the establishment of the novel therapeutics.

1) Molecular mechanisms of type 2 diabetes

We have been attempting to elucidate the mechanisms underlying the development of type 2 diabetes at the molecular and genetic levels. To this end, in collaboration with RIKEN and several cohorts, we explored the comprehensive catalog of genomic variations to identify variations conferring susceptibility to type 2 diabetes in the Japanese population. We are also exploring the signal transduction pathways and physiological roles of insulin and adipokines in various tissues and the mechanisms of insulin secretion under the normal or pathological conditions, such as diabetes and obesity disease, using a number of transgenic and knockout animal models,

in parallel with information obtained by whole-genome analysis of human patients. In particular, we are interested in the physiological and pathophysiological functions of adipokines secreted by adipocytes, including adiponectin, and the signal transduction pathway of adiponectin through the receptors, AdipoR1 and AdipoR2, that we discovered and characterized. We have also identified “AdipoRon” as an adiponectin receptor agonist, which will contribute to the development and optimization of AdipoR-targeted therapeutics. In addition, we have been successfully unraveling the molecular mechanisms of inter-tissue communication of glucose metabolism in obesity disease, pancreatic β -cell proliferation and insulin secretion, and brown and white adipocyte-specific transcriptional and epigenetic regulations in obesity. Recently, we are also investigating regulatory mechanisms of intestinal epithelial stem cells using in vitro organoid culture system. We believe that these findings and research activities will lead to novel therapeutic strategies for diabetes and the metabolic syndrome.

2) Pathophysiological roles of lipid storage and atherosclerosis

Our aim is to clarify the significance of metabolic risk factors in the onset and development of atherosclerosis. We are currently investigating the pathophysiological roles of lipid storage in obesity disease, fatty liver, diabetes, dyslipidemia and atherosclerosis using strategies of molecular biology and genetic engineering techniques. Utilizing the animal models of lipid disorders and molecular biological technique, we are analyzing the roles of lipid transporters, nuclear receptors and the anti-oxidative proteins on the lipid disorders and atherosclerosis. We are currently interested in the cholesterol and lipid absorption from the intestine and lipid handling in the cells.

3) Clinical trials and epidemiological studies

We are conducting clinical trials and epidemiological studies including “Japan Diabetes Optimal Integrated Treatment study for 3 major risk factors of cardiovascular diseases (J-DOIT3)” follow-up study, “Japan Diabetes compREhensive database project based on an Advanced electronic Medical record

System (J-DREAMS)”, database project on obesity (J-ORBIT), National Database project, systematic reviews and meta-analyses with a focus on important issues such as metabolic syndrome. Through investigator initiated clinical trials, we have been investigating anti-aging effect of Nicotinamide mononucleotide on systemic metabolism, biomarkers of oxidative stress, a non-invasive method for evaluating glycemic control, and a new class of anti-diabetic agents.

References

1. Aihara M, Jinnouchi H, Yoshida A, Ijima H, Sakurai Y, Hayashi T, Koizumi C, Kubota T, Usami S, Yamauchi T, Sakata T, Kadowaki T, Kubota N. Evaluation of glycated albumin levels in tears and saliva as a marker in patients with diabetes mellitus. *Diabetes Res Clin Pract.* 2023 May;199:110637. doi: 10.1016/j.diabres.2023.110637. Epub 2023 Mar 22. PMID: 36963507.
2. Aihara M, Hayashi T, Koizumi C, Sakurai Y, Sawada M, Kubota T, Kadowaki T, Yamauchi T, Kubota N. Bi-weekly Glycated Albumin Measurement was Useful to Encourage Behavioral Changes in People with Type 2 Diabetes Mellitus. *Diabetes Ther.* 14:1711-1721,2023
3. Aihara M, Doi S, Kubota N, Ohe K, Ohkuma K, Sawada M, Sekine R, Usami S, , Yamauchi T. Impact of the COVID-19 pandemic on the glycemic control in people with diabetes mellitus: A retrospective cohort study. *J Diabetes Investig.* 2023 Aug;14(8):985-993. doi: 10.1111/jdi.14021. Epub 2023 Apr 28. PMID: 37118898; PMCID: PMC10360387.
4. Appenzeller-Herzog C, Rosat A, Mathes T, Baroja-Mazo A, Chruscinski A, Feng S, Herrero I, Londono MC, Mazariegos G, Ohe H, Pons JA, Sanchez-Fueyo A, Waki K, Vionnet J. Time since liver transplant and immunosuppression withdrawal outcomes: Systematic review and individual patient data meta-analysis. *Liver Int.* 2023 Oct 31. doi: 10.1111/liv.15764.
5. Asahara N, Okada-Iwabu M, Iwabu M, Wada K, Oka K, Yamauchi T, Kadowaki T. A monoclonal antibody activating AdipoR for type 2 diabetes and nonalcoholic steatohepatitis. *Sci Adv.* 9:

- eadg4216, 2023
6. Hayashi T, Wada N, Kubota T, Koizumi C, Sakurai Y, Aihara M, Usami S, Yamauchi T, Kubota N. Associations of sleep quality with the skeletal muscle strength in patients with type 2 diabetes with poor glycemic control. *J Diabetes Investig.* 14:801-810,2023
 7. Hiraike Y, Saito K, Oguchi M, Wada T, Toda G, Tsutsumi S, Bando K, Sagawa J, Nagano G, Ohno H, Kubota N, Kubota T, Aburatani H, Kadowaki T, Waki H, Yanagimoto S, Yamauchi T. NFIA in adipocytes reciprocally regulates mitochondrial and inflammatory gene program to improve glucose homeostasis. *Proc Natl Acad Sci U S A.* 120: e2308750120, 2023
 8. Igarashi M, Yamauchi T. Insight into the application of nicotinamide mononucleotide (NMN) to age-related disorders. *J Cell Mol Immunol.* 2(1):9-13,2023.
 9. Ihana-Sugiyama N, Sugiyama T, Hirano T, Imai K, Ohsugi M, Kawasaki R, Murata T, Ogura Y, Ueki K, Yamauchi T, Kadowaki T. Patient referral flow between physician and ophthalmologist visits for diabetic retinopathy screening among Japanese patients with diabetes: A retrospective cross-sectional cohort study using the National Database. *J Diabetes Investig.* 14:883-892, 2023
 10. Kobori T, Onishi Y, Yoshida Y, Tahara T, Kikuchi T, Kubota T, Iwamoto M, Sawada T, Kobayashi R, Fujiwara H, Kasuga M: Association of glucagon-like peptide-1 receptor agonist treatment with gastric residue in an esophagogastroduodenoscopy. *J Diabetes Investig.* 14: 767-773, 2023.
 11. Miura M, Igarashi M, Isotani R, Nakagawa-Nagahama Y, Kuranami S, Naruse K, Kadowaki T, Yamauchi T, SIRT1 Controls Enteroendocrine Progenitor Cell Proliferation in High-Fat Diet-Fed Mice. *Cell Mol Gastroenterol Hepatol.* S2352-345X(23)00151-0, 2023
 12. Odawara S, Shimbo T, Yamauchi T, Kobayashi D. Association of Low-Normal Free T4 Levels With Future Major Depression Development. *J Endocr Soc.* 7: bvad096,2023
 13. Ohkuma K, Sawada M, Aihara M, Doi S, Sekine R, Usami S, Ohe K, Kubota N, Yamauchi T. Impact of the COVID-19 pandemic on the glycemic control in people with diabetes mellitus: A retrospective cohort study. *J Diabetes Investig.* 14:985-993,2023
 14. Okada A, Yamaguchi S, Imaizumi T, Oba K, Kurakawa KI, Yamauchi T, Kadowaki T, Nangaku M. Modification effects of albuminuria on the association between kidney function and development of anemia in diabetes. *J Clin Endocrinol Metab.* dgad660, 2023
 15. Okada A, Kaneko H, Matsuoka S, Itoh H, Suzuki Y, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Yamaguchi S, Node K, Yamauchi T, Yasunaga H, Komuro I. Association of cardiovascular health metrics with annual incidence of prediabetes or diabetes: Analysis of a nationwide real-world database. *J Diabetes Investig.* 14:452-462, 2023
 16. Okada A, Yamada G, Kimura T, Hagiwara Y, Yamaguchi S, Kurakawa KI, Nangaku M, Yamauchi T, Matsuyama Y, Kadowaki T. Diagnostic ability using fatty liver and metabolic markers for metabolic-associated fatty liver disease stratified by metabolic/glycemic abnormalities. *J Diabetes Investig.* 14:463-478,2023
 17. Okada A, Yamana H, Pan R, Yamaguchi S, Kumazawa R, Matsui H, Fushimi K, Honda Y, Nangaku M, Yamauchi T, Yasunaga H, Kadowaki T, Kim Y. Effect modification of the association between temperature variability and hospitalization for cardiovascular disease by comorbid diabetes mellitus: A nationwide time-stratified case-crossover analysis. *Diabetes Res Clin Pract.* 3; 202:110771, 2023
 18. Saito K, Hiraike Y, Oguchi M, Yamauchi T. Semi-Automated Isolation of the Stromal Vascular Fraction from Murine White Adipose Tissue Using a Tissue Dissociator. *J Vis Exp.* 19;(195),2023
 19. Sankoda A, Nagae Y, Waki K, Sze WT, Oba K, Mieno M, Nangaku M, Yamauchi T, Ohe K. Glycemic control, renal progression, and usage of telemedicine phone consultations among Japanese type 2 diabetes mellitus patients during the COVID-19 pandemic: a retrospective cohort study. *JMIR Diabetes.* 2023 doi: 10.2196/42607. Online ahead of print.

20. Sato M, Toyoshima K, Tamura Y, Araki A. Spontaneous pneumoperitoneum and diabetic ketoacidosis in fulminant type 1 diabetes: a case report. *Oxf Med Case Reports*. 2023 Aug 20; 2023(8):omad079.
21. Sato M, Tamura Y, Murao Y, Yorikawa F, Katsumata Y, Watanabe S, Zen S, Kodera R, Oba K, Toyoshima K, Chiba Y, Araki A. The cross-sectional area of erector spinae muscle and the liver-to-spleen ratio are associated with frailty in older patients with diabetes: a cross-sectional study. *BMC Geriatr*. 2023 Nov 22; 23(1):765.
22. Shibuta T, Waki K, Miyake K, Igarashi A, Yamamoto-Mitani N, Sankoda A, Takeuchi Y, Sumitani M, Yamauchi T, Nangaku M, Ohe K. Preliminary Efficacy, Feasibility, and Perceived Usefulness of a Smartphone-Based Self-Management System With Personalized Goal Setting and Feedback to Increase Step Count Among Workers With High Blood Pressure: Before-and-After Study. *MIR Cardio*. 7:e43940. doi: 10.2196/43940,2023
23. Soeda K, Sasako T, Enooku K, Kubota N, Kobayashi N, Ikushima YM, Awazawa M, Bouchi R, Toda G, Yamada T, Nakatsuka T, Tateishi R, Kakiuchi M, Yamamoto S, Tatsuno K, Atarashi K, Suda W, Honda K, Aburatani H, Yamauchi T, Fujishiro M, Noda T, Koike K, Kadowaki T, Ueki K. Gut insulin action protects from hepatocarcinogenesis in diabetic mice comorbid with nonalcoholic steatohepatitis. *Nat Commun*. 14:6584, 2023
24. Sze WT, Waki K, Enomoto S, Nagata Y, Nangaku M, Yamauchi T, Ohe K. Step Add: A personalized mHealth intervention based on social cognitive theory to increase physical activity among type 2 diabetes patients. *J Biomed Inform*. 145:104481,2023
25. Tanaka M, Takase S, Ishiura H, Yamauchi T, Okazaki S, Okazaki H, A novel homozygous nonsense variant of LMF1 in pregnancy-induced hypertriglyceridemia with acute pancreatitis. *J Clin Lipidol*. 17:327-331, 2023
26. Yamaguchi S, Atarashi T, Okada A, Nasu S, Yamauchi T, Arase Y, Aizawa T, Nangaku M, Kadowaki T. Impact of the COVID-19 Pandemic on Health Check-ups: A Nationwide Questionnaire Survey in 639 Healthcare Facilities in Japan Society of Ningen Dock. *JMA J*. 2023 Jul 14; 6(3):321-331.
27. Yeung AM, Huang J, Pandey A, Hashim IA, Kerr D, Pop-Busui R, Rhee CM, Shah VN, Bally L, Bayes-Genis A, Bee YM, Bergenstal R, Butler J, Fleming GA, Gilbert G, Greene SJ, Kosiborod MN, Leiter LA, Mankovsky B, Martens TW, Mathieu C, Mohan V, Patel KV, Peters A, Rhee EJ, Rosano GMC, Sacks DB, Sandoval Y, Seley JJ, Schnell O, Umpierrez G, Waki K, Wright EE Jr, Wu AHB, Klonoff DC. Biomarkers for the diagnosis of heart failure in people with diabetes: A consensus report from diabetes technology society. *Prog Cardiovasc Dis*. 2023 May 11: S0033-0620(23)00050-6.
28. Effects of empagliflozin on progression of chronic kidney disease: a prespecified secondary analysis from the empa-kidney trial. EMPA-KIDNEY Collaborative Group. *Lancet Diabetes Endocrinol*. 12:39-50, 2024
29. Iijima H, Shimizu H, Mori-Anai K, Kawaguchi A, Mochida Y, Yamauchi T, Kadowaki T. Publisher Correction: Evaluation of Age-Related Changes in Teneligliptin Pharmacokinetics in Japanese and European Descent Subjects Using a Physiologically Based Pharmacokinetic Model. *Diabetes Ther*. 15:763-777, 2024
30. Impact of primary kidney disease on the effects of empagliflozin in patients with chronic kidney disease: secondary analyses of the EMPA-KIDNEY trial. EMPA-KIDNEY Collaborative Group. *Lancet Diabetes Endocrinol*. 12:51-60, 2024
31. Katsumata Y, Toyoshima K, Tamura Y, Murao Y, Sato M, Watanabe S, Kodera R, Oba K, Ishikawa J, Chiba Y, Awata S, Araki A: Categorization using the Dementia Assessment Sheet for Community-Based Integrated Care System 8-items (DASC-8) based on cognitive function and activities of daily living predicts frailty, disability and mortality in older adults. *Geriatr. Gerontol. Int*. 2024; 24: 150–155.
32. Ken Suzuki, Konstantinos Hatzikotoulas, Lorraine Southam, Henry J Taylor, Xianyong Yin, Kim M Lorenz, Ravi Mandla, Alicia Huerta-

Chagoya, Nigel W Rayner, Ozvan Bocher, S V Arruda Ana Luiza de, Kyuto Sonehara, Shinichi Namba, Simon S K Lee, Michael H Preuss, Lauren E Petty, Philip Schroeder, Brett Vanderwerff, Mart Kals, Fiona Bragg, Kuang Lin, Xiuqing Guo, Weihua Zhang, Jie Yao, Young Jin Kim, Mariaelisa Graff, Fumihiko Takeuchi, Jana Nano, Amel Lamri, Masahiro Nakatochi, Sanghoon Moon, Robert A Scott, James P Cook, Jung-Jin Lee, Ian Pan, Daniel Taliun, Esteban J Parra, Jin-Fang Chai, Lawrence F Bielak, Yasuharu Tabara, Yang Hai, Gudmar Thorleifsson, Niels Grarup, Tamar Sofer, Matthias Wuttke, Chloé Sarnowski, Christian Gieger, Darryl Nosome, Stella Trompet, Soo-Heon Kwak, Jirong Long, Meng Sun, Lin Tong, Wei-Min Chen, Suraj S Nongmaithem, Raymond Noordam, Victor J Y Lim, Claudia H T Tam, Yoonjung Yoonie Joo, Chien-Hsiun Chen, Laura M Raffield, Bram Peter Prins, Aude Nicolas, Lisa R Yanek, Guanjie Chen, Jennifer A Brody, Edmond Kabagambe, Ping An, Anny H Xiang, Hyeok Sun Choi, Brian E Cade, Jingyi Tan, K Elaine Broadaway, Alice Williamson, Zoha Kamali, Jinrui Cui, Linda S Adair, Adebawale Adeyemo, Carlos A Aguilar-Salinas, Tarunveer S Ahluwalia, Sonia S Anand, Alain Bertoni, Jette Bork-Jensen, Ivan Brandslund, Thomas A Buchanan, Charles F Burant, Adam S Butterworth, Mickaël Canouil, Juliana C N Chan, Li-Ching Chang, Miao-Li Chee, Ji Chen, Shyh-Huei Chen, Yuan-Tsong Chen, Zhengming Chen, Lee-Ming Chuang, Mary Cushman, John Danesh, Swapan K Das, H Janaka de Silva, George Dedoussis, Latchezar Dimitrov, Ayo P Doumatey, Shufa Du, Qing Duan, Kai-Uwe Eckardt, Leslie S Emery, Daniel S Evans, Michele K Evans, Krista Fischer, James S Floyd, Ian Ford, Oscar H Franco, Timothy M Frayling, Barry I Freedman, Pauline Genter, Hertz C Gerstein, Vilmantas Giedraitis, Clicerio González-Villalpando, Maria Elena González-Villalpando, Penny Gordon-Larsen, Myron Gross, Lindsay A Guare, Sophie Hackinger, Sohee Han, Andrew T Hattersley, Christian Herder, Momoko Horikoshi, Annie-Green Howard, Willa Hsueh, Mengna Huang, Wei Huang, Yi-Jen Hung, Mi Yeong Hwang,

Chii-Min Hwu, Sahoko Ichihara, Mohammad Arfan Ikram, Martin Ingelsson, Md Tariqul Islam, Masato Isono, Hye-Mi Jang, Farzana Jasmine, Guozhi Jiang, Jost B Jonas, Torben Jørgensen, Fouad R Kandeel, Anuradhani Kasturiratne, Tomohiro Katsuya, Varinderpal Kaur, Takahisa Kawaguchi, Jacob M Keaton, Abel N Kho, Chiea-Chuen Khor, Muhammad G Kibriya, Duk-Hwan Kim, Florian Kronenberg, Johanna Kuusisto, Kristi Läll, Leslie A Lange, Kyung Min Lee, Myung-Shik Lee, Nanette R Lee, Aaron Leong, Liming Li, Yun Li, Ruifang Li-Gao, Symen Lithgart, Cecilia M Lindgren, Allan Linneberg, Ching-Ti Liu, Jianjun Liu, Adam E Locke, Tin Louie, Jian'an Luan, Andrea O Luk, Xi Luo, Jun Lv, Julie A Lynch, Valeriya Lyssenko, Shiro Maeda, Vasiliki Mamakou, Sohail Rafik Mansuri, Koichi Matsuda, Thomas Meitinger, Andres Metspalu, Huan Mo, Andrew D Morris, Jerry L Nadler, Michael A Nalls, Uma Nayak, Ioanna Ntalla, Yukinori Okada, Lorena Orozco, Sanjay R Patel, Snehal Patil, Pei Pei, Mark A Pereira, Annette Peters, Fraser J Pirie, Hannah G Polikowsky, Bianca Porneala, Gauri Prasad, Laura J Rasmussen-Torvik, Alexander P Reiner, Michael Roden, Rebecca Rohde, Katheryn Roll, Charumathi Sabanayagam, Kevin Sandow, Alagu Sankareswaran, Naveed Sattar, Sebastian Schönherr, Mohammad Shahriar, Botong Shen, Jinxiu Shi, Dong Mun Shin, Nobuhiro Shojima, Jennifer A Smith, Wing Yee So, Alena Stančáková, Valgerdur Steinthorsdottir, Adrienne M Stilp, Konstantin Strauch, Kent D Taylor, Barbara Thorand, Unnur Thorsteinsdottir, Brian Tomlinson, Tam C Tran, Fuu-Jen Tsai, Jaakko Tuomilehto, Teresa Tusie-Luna, Miriam S Udler, Adan Valladares-Salgado, Rob M van Dam, Jan B van Klinken, Rohit Varma, Niels Wachter-Rodarte, Eleanor Wheeler, Ananda R Wickremasinghe, Ko Willems van Dijk, Daniel R Witte, Chittaranjan S Yajnik, Ken Yamamoto, Kenichi Yamamoto, Kyunghoon Yoon, Canqing Yu, Jian-Min Yuan, Salim Yusuf, Matthew Zawistowski, Liang Zhang, Wei Zheng; VA Million Veteran Program, AMED GRIFIN Diabetes Initiative Japan; Biobank Japan Project, Penn Medicine BioBank, Regeneron Genetics

- Center, eMERGE Consortium; International Consortium for Blood Pressure (ICBP); Meta-Analyses of Glucose and Insulin-Related Traits Consortium (MAGIC); Leslie J Raffel, Michiya Igase, Eli Ipp, Susan Redline, Yoon Shin Cho, Lars Lind, Michael A Province, Myriam Fornage, Craig L Hanis, Erik Ingelsson, Alan B Zonderman, Bruce M Psaty, Ya-Xing Wang, Charles N Rotimi, Diane M Becker, Fumihiko Matsuda, Yongmei Liu, Mitsuhiro Yokota, Sharon L R Kardia, Patricia A Peyser, James S Pankow, James C Engert, Amélie Bonnefond, Philippe Froguel, James G Wilson, Wayne H H Sheu, Jer-Yuarn Wu, M Geoffrey Hayes, Ronald C W Ma, Tien-Yin Wong, Dennis O Mook-Kanamori, Tiinamaija Tuomi, Giriraj R Chandak, Francis S Collins, Dwaipayan Bharadwaj, Guillaume Paré, Michèle M Sale, Habibul Ahsan, Ayesha A Motala, Xiao-Ou Shu, Kyong-Soo Park, J Wouter Jukema, Miguel Cruz, Yii-Der Ida Chen, Stephen S Rich, Roberta McKean-Cowdin, Harald Grallert, Ching-Yu Cheng, Mohsen Ghanbari, E-Shyong Tai, Josee Dupuis, Norihiro Kato, Markku Laakso, Anna Köttgen, Woon-Puay Koh, Donald W Bowden, Colin N A Palmer, Jaspal S Kooner, Charles Kooperberg, Simin Liu, Kari E North, Danish Saleheen, Torben Hansen, Oluf Pedersen, Nicholas J Wareham, Juyoung Lee, Bong-Jo Kim, Iona Y Millwood, Robin G Walters, Kari Stefansson, Mark O Goodarzi, Karen L Mohlke, Claudia Langenberg, Christopher A Haiman, Ruth J F Loos, Jose C Florez, Daniel J Rader, Marylyn D Ritchie, Sebastian Zöllner, Reedik Mägi, Joshua C Denny, Toshimasa Yamauchi, Takashi Kadowaki, John C Chambers, Maggie C Y Ng, Xueling Sim, Jennifer E Below, Philip S Tsao, Kyong-Mi Chang, Mark I McCarthy, James B Meigs, Anubha Mahajan, Cassandra N Spracklen, Josep M Mercader, Michael Boehnke, Jerome I Rotter, Marijana Vujkovic, Benjamin F Voight, Andrew P Morris, Eleftheria Zeggini. Genetic drivers of heterogeneity in type 2 diabetes pathophysiology. *Nature*. 627:347-357, 2024
33. Kobori T, Iwabu M, Okada-Iwabu M, Ohuchi N, Kikuchi A, Yamauchi N, Kadowaki T, Yamauchi T, Kasuga M. Decreased AdipoR1 signaling and its implications for obesity-induced male infertility. *Sci Rep*. 4:5701, 2024
 34. Ogura M, Okazaki S, Okazaki H, Tada H, Dobashi K, Nakamura K, Matsunaga K, Miida T, Minamino T, Yokoyama S, Harada-Shiba M.: Transitional Medicine of Intractable Primary Dyslipidemias in Japan. *J Atheroscler Thromb*. 2024 Mar 26. doi: 10.5551/jat.RV22016. Online ahead of print.
 35. Okada A, Yamaguchi S, Ono S, Kurakawa KI, Yasunaga H, Nangaku M, Yamauchi T, Kadowaki T. Modification effect of receipt of diabetes care on the association between COVID-19 infection and HbA1c level during the first year of the coronavirus pandemic using a nationwide population-based database. *J Diabetes Investig*. doi: 10.1111/jdi.14171, 2024
 36. Okada A, Honda A, Watanabe H, Sasabuchi Y, Aso S, Kurakawa KI, Nangaku M, Yamauchi T, Yasunaga H, Chikuda H, Kadowaki T, Yamaguchi S. Proteinuria screening and risk of bone fracture: a retrospective cohort study using a nationwide population-based database. *Clin Kidney J*. 17: sfad302, 2024
 37. Saito R, Sze WT, Waki K, Enomoto S, Yamauchi T, Nangaku M, Ohe K. Effect of Step Count Measurement on Glycemic Control: Secondary Analysis of a Randomized Controlled Trial. *Stud Health Technol Inform*. 310:549-553, 2024
 38. Sakurai Y, Kubota N, Takamoto I, Wada N, Aihara M, Hayashi T, Kubota T, Hiraike Y, Sasako T, Nakao H, Aiba A, Chikaoka Y, Kawamura T, Kadowaki T, Yamauchi T. Overexpression of UBE2E2 in Mouse Pancreatic β -Cells Leads to Glucose Intolerance via Reduction of β -Cell Mass. *Diabetes*. 73:474-489, 2024
 39. Sasako T, Suzuki K, Odawara S, Suwanai H, Akuta N, Kubota N, Ueki K, Kadowaki T, Yamauchi T. Corticosteroid-triggered acute skeletal muscle loss in lipodystrophy: A case report. *J Diabetes Investig*. doi: 10.1111/jdi.14158, 2024
 40. Shojima N, Yamauchi T. Common metabolite for microangiopathy in Japanese and European populations. *J Diabetes Investig*. 2024 Mar 22.

doi: 10.1111/jdi.14189. Epub ahead of print.
2024.3

41. Waki K, Tsurutani Y, Waki H, Enomoto S, Kashiwabara K, Fujiwara A, Orime K, Kinguchi S, Yamauchi T, Hirawa N, Tamura K, Terauchi Y, Nangaku M, Ohe K. Efficacy of StepAdd, a Personalized mHealth Intervention Based on Social Cognitive Theory to Increase Physical Activity Among Patients With Type 2 Diabetes Mellitus: Protocol for a Randomized Controlled Trial. JMIR Res Protoc. 13: e53514, 2024

Department of Hematology and Oncology

Professor

Mineo Kurokawa, M.D., Ph.D.

Lecturer

Yosuke Masamoto, M.D., Ph.D.,

Ken Morita, M.D., Ph.D

Assistant Professor

Hiroaki Maki, M.D., Ph.D.

Akira Honda, M.D., Ph.D.,

Arika Shimura, M.D., Ph.D.

Megumi Yasunaga, M.D., Ph.D.,

Masami Ozu, M.D., Ph.D.

Homepage <http://www.u-tokyo-hemat.com/>

Introduction and Organization

The Department of Hematology and Oncology is responsible for clinical activities in outpatient as well as inpatient clinics of hematological disorders, research activities for hematology/oncology, and education of undergraduate as well as graduate students. We are also engaged in continuous education of post-graduate doctors who develop into sophisticated hematologists of eminent distinction. These activities are performed by the united efforts of all members who belong to the department. Dr. Mineo Kurokawa was assigned as Professor of the Department of Hematology and Oncology in 2005. Other staff of our department consists of 2 lecturers and 5 assistant professors.

Clinical activities

On the average, 50-70 patients with hematological diseases are treated in the ward. Clinical facilities include patient rooms with high-efficiency particulate air filtration and filtrated water supply. Patients who are eligible for the treatment with high-grade infection prophylaxis are admitted to the facilities. Patient care is provided by team management. That is, three doctors (a junior resident, a senior resident, and an assistant

professor) are assigned to a single patient. Since clinical issues are highly related to hematopoietic stem cell transplantation especially for patients with hematological diseases, a substantial portion of our clinical conferences are shared with staff members of the Department of Cell Therapy and Transplantation Medicine and the Department of Pediatrics (Hematology/Oncology). Many problems arising in daily clinical practice are discussed in the morning clinical conference held thrice a week. Diagnostic and therapeutic issues as well as pathological aspects of indicative and/or educational cases are discussed in clinical conferences held twice a month.

Outpatient clinical services are provided from Monday to Friday in the morning and afternoon using three booths. Approximately 70-80 patients visit our outpatient clinic every weekday. One of our ultimate goals in the clinical activities is to cure patients with hematological malignancies.

We perform various kinds of genetic or molecular tests to detect, characterize, and monitor neoplastic cells and their results are used in the diagnosis and treatment.

Here we introduce technical aspects on the treatment strategy:

1. High dose chemotherapy with autologous stem cell

transplant: High-dose chemotherapy is administered for the treatment of hematological neoplasms and solid tumors. For the autologous stem cell support, peripheral blood stem cell is usually selected as a source of stem cells. Recently, we are actively performing autologous transplantation as a treatment for CNS malignant lymphoma, which is considered intractable, to improve the prognosis.

2. **Allogeneic hematopoietic stem cell transplant:** Bone marrow cells are harvested from healthy donors by operation under general anesthesia and immediately infused to a recipient. Peripheral blood stem cells (PBSCs) are harvested from healthy donors by leukapheresis using an automated continuous flow blood cell separator. PBSCs are immediately infused to a recipient or preserved in liquid nitrogen in cooperation with the Department of Transfusion Medicine. Allogeneic transplant with non-myeloablative conditioning (also referred to as reduced-intensity stem cell transplant (RIST)) is commonly performed for elderly patients and patients with impaired organ function. HLA-haploidentical hematopoietic stem cell transplantation is also ready to be performed to patients if necessary. Allogeneic hematopoietic stem cell transplant for the elderly is performed under the admission of Patient Relations and Clinical Ethics Center. Cord blood cells are also used as a source of hematopoietic stem cells.
3. **CAR-T Cell Therapy:** T cells that are collected from the patients are genetically treated in the lab to produce special receptors called chimeric antigen receptors, or CARs. These CARs allow the T cells to recognize an antigen at the surface of lymphoma cells and activate T cells' ability to kill these tumor cells. By collaborating with the Department of Cell Therapy and Transplantation Medicine, the Department of Pediatrics (Hematology/Oncology), and the Cell Processing Center, we have installed a capacity to perform this most advanced and promising cancer treatment for patients with hematologic malignancies, and actively recruiting patients.

Teaching activities

A lecture course on etiology, pathogenesis, clinical

and laboratory features, differential diagnosis, therapy and prognosis for all hematological diseases is provided for the second-grade medical students. The course contents include:

1. Mechanisms of hematopoiesis, transplantation medicine and cell therapy
2. Acute leukemia and myeloproliferative disorders
3. Bone marrow failure syndrome (aplastic anemia and myelodysplastic syndrome)
4. Lymphoma and myeloma
5. Hemostasis and thrombosis
6. Hemolytic anemia and anemia of various causes

Clinical clerkships on diagnostic and therapeutic issues and arts are given for the third-grade medical students on a man-to-man basis with a senior faculty member who is erudite both in general internal medicine and in hematology and oncology. During the course, students are required to learn the basic techniques of medical interview and physical examination, interpretation of laboratory tests, and practical medical procedures.

Undergraduate students are educated to become independent researchers both in basic and clinical research.

Education of clinical fellows to train hematologists is also provided. They are trained to achieve knowledge and techniques necessary for hematologists in our hospital and encouraged to present clinical studies at academic meetings.

Research activities

The major research projects are as follow: (1) molecular mechanisms of hematopoietic neoplasms, (2) hematopoietic transcription factors, (3) signal transduction in hematopoietic cells, (4) chromosomal and genomic approaches to leukemogenesis, (5) generation of murine models for leukemias, (6) reprogramming of leukemic cells into iPS cells, and functional analysis using iPS cells, (7) regulation of hematopoiesis. (8) genetic and pathological mechanism of Erdheim-Chester disease. Translational research to develop novel methods for diagnosis and treatment based on basic research is also performed. Every effort has been made to achieve the highest quality in both clinical and basic medical research. The ultimate aims of our research are the application of epoch-making

discoveries in research fields to the clinical hematology and oncology. Representative publications from our departments published in the past year are listed in the reference.

References

1. Masuda Y, Oyama T, Nakazaki K, Nakai Y, Sasaki K, Matsuda K, Masamoto Y, and Kurokawa M. Aortitis associated with prophylactic short-acting granulocyte colony-stimulating factor administration: a case report and review of the literature. *Internal Medicine* 62(11): 1647-1652, 2023.
2. Oyama T, Taoka K, Chiba A, Masamoto Y, Ikemura M, Honda A, Maki H, and Kurokawa M. Daratumumab plus lenalidomide and dexamethasone for relapsed POEMS syndrome with bone plasmacytoma harboring 17p deletion. *International Journal of Hematology* 117(3): 463-467, 2023.
3. Masamoto Y, Chiba A, Mizuno H, Hino T, Hayashida H, Sato T, Bando M, Shirahige K, and Kurokawa M. EVI1 exerts distinct roles in AML via ERG and cyclin D1 promoting a chemoresistance and immune-suppressive environment. *Blood Advances* 7(8): 1577-1593, 2023.
4. Oyama T, Matsuda K, Honda A, Maki H, Masamoto Y, Murakami D, Toya T, Sakurai M, Kataoka K, Doki N, and Kurokawa M. Clinical characteristics of steroid-responsive but dependent chronic graft-versus-host disease: a multicenter retrospective analysis. *International Journal of Hematology* 117(2): 260-268, 2023.
5. Matsuda K, Oyama T, Maki H, Nakazaki K, Yasunaga M, Honda A, Masamoto Y, and Kurokawa M. Prompt initiation of conventional chemotherapy to avoid early death in patients with newly diagnosed acute promyelocytic leukemia. *Internal Medicine* 62(15): 2181-2185, 2023.
6. Masamoto Y, Shimura A, Honda A, Taoka K, Maki H, and Kurokawa M. Obinutuzumab and reduced bendamustine is effective for elderly patients with follicular lymphoma. *Annals of Hematology* 102(1): 243-244, 2023.
7. Yoshida M, Morita K, Fukushima H, Jona M, Nishikawa M, Yatomi Y, Kishino Y, Iwasaki A, Ushiku T, Imadome K, Honda A, Maki H, and Kurokawa M. Development of Epstein-Barr virus-associated lymphoproliferative disorder and hemophagocytic lymphohistiocytosis during long-term lenalidomide maintenance therapy in multiple myeloma. *International Journal of Hematology* 117(5): 769-773, 2023.
8. Yoshida M, Matsuda K, Endo K, Honda A, Maki H, Taoka K, Masamoto Y, Wakimoto Y, Jubishi D, Moriya K, and Kurokawa M. Toxic shock like syndrome caused by *Streptococcus agalactiae* bacteremia during treatment for multiple myeloma. *Journal of Infection and Chemotherapy* 29(4): 407-409, 2023.
9. Kanda Y, Usuki K, Inagaki M, Ohta A, Ogasawara Y, Obara N, Kako S, Kurokawa M, Shimada N, Suzuki T, Hama A, Yamaguchi H, Nakao S, and Yamazaki H. Decision analysis of allogeneic bone marrow transplantation versus immunosuppressive therapy for young adult patients with aplastic anemia. *International Journal of Hematology* 117(5): 660-668, 2023.
10. Yoshida M, Matsuda K, Taoka K, Honda A, Maki H, Masamoto Y, Jona M, Nishikawa M, Yatomi Y, and Kurokawa M. Expansion of large granular lymphocytes after autologous hematopoietic stem cell transplantation. *International Journal of Hematology* 117(6): 839-844, 2023.
11. Obo T, Morita K, Sumida Y, Nakazaki-Watadani K, Ikemura M, Yasaka K, Abe O, Takami H, Takayanagi S, Tanaka S, Maki H, Masamoto Y, Miwa A and Kurokawa M. Isolated relapse of plasma cell leukemia in the central nervous systems, a case report and literature review. *International Journal of Hematology* 118(1): 135-140, 2023.
12. Murayama R, Abe-Doi M, Masamoto Y, Kashiwabara K, Komiyama C, Sanada H, and Kurokawa M. Verification study on the catheterization of an upper arm vein using the new long peripheral intravenous catheter to reduce catheter failure incidence: A randomized controlled trial. *Drug Discoveries and Therapeutics* 17(1): 52-59, 2023.
13. Fukushima H, Morita K, Ikemura M, Tanaka M, Nakai Y, Maki H, Suzuki T, Mizuno S, Nakai Y, and Kurokawa M. Acute pancreatitis as the initial manifestation of acute myeloid leukemia with

- chromosome 16 rearrangements. *International Journal of Hematology* 118(3): 381-387, 2023.
14. Nishimura H, Ikawa Y, Kajikawa E, Shimizu-Mizuno N, Kitajima T, Nikaido I, Kurokawa M, Watanabe T and Hamada H. Maternal epigenetic factors in embryonic and postnatal development. *Genes to Cells* 28(6): 422-432, 2023.
 15. Mitsutake A, Iwata A, Ishiura H, Mitsui J, Mori H, Toya T, Honda A, Kurokawa M, Sakai N, Tsuji S, and Toda T. Favorable outcome of hematopoietic stem cell transplantation in late-onset Krabbe disease. *Brain and Development* 45(7): 408-412, 2023.
 16. Miyashita D, Sayama S, Iriyama T, Nakazaki K, Toshimitsu M, Seyama T, Kumasawa K, Nagamatsu T, Kurokawa M, and Osuga Y. Immune thrombocytopenic purpura with chronic hypertension treated with eltrombopag during pregnancy which developed leukocytosis and superimposed preeclampsia. *Oxford Medical Case Reports* 2023(5): omad047, 2023.
 17. Hoshino Y, Manaka K, Sato J, Asatsuma Y, Hori-koshi H, Takeuchi M, Ito N, Fujita M, Yasunaga M, Matsuda K, Honda A, Maki H, Masamoto Y, Kurokawa M, Nangaku M, and Makita N. Recurrent bilateral adrenal infarction with myelodysplastic/myeloproliferative neoplasm-unclassifiable (MDS/MPN-U): a case report. *BMC Endocrine Disorders* 23(1): 128, 2023.
 18. Homan CC, Drazer MW, Yu K, Lawrence DM, Feng J, Arriola-Martinez L, Pozsgai MJ, McNeely KE, Ha T, Venugopal P, Arts P, King-Smith SL, Cheah J, Armstrong M, Wang P, Böddör C, Cantor AB, Cazzola M, Degelman E, DiNardo CD, Duplez N, Favier R, Fröhling S, Rio-Machin A, Klco JM, Krämer A, Kurokawa M, Lee J, Malcovati L, Morgan NV, Natsoulis G, Owen C, Patel KP, Preudhomme C, Raslova H, Rienhoff H, Ripperger T, Schulte R, Tawana K, Velloso E, Yan B, Erika Kim42, Sood R, NISC Comparative Sequencing Program, Hsu AP, Holland SM, Phillips K, Poplawski NK, Babic M, Wei AH, Forsyth C, Fan HM, Lewis ID, Cooney J, Susman R, Fox LC, Blombery P, Singhal D, Hiwase D, Phipson B, Schreiber AW, Hahn CN, Scott HS, Liu P, Godley LA, and Brown AL. Somatic mutational landscape of hereditary hematopoietic malignancies caused by germline variants in RUNX1, GATA2, and DDX41. *Blood Advances* 7(20): 6092-6107, 2023.
 19. Oyama T, Yasunaga M, Jona M, Nishikawa M, Yatomi Y, Honda A, Maki H, Masamoto Y, Morita K, and Kurokawa M. Successful treatment with acalabrutinib and steroid for autoimmune thrombocytopenia due to relapsed chronic lymphocytic leukemia with severe bone marrow infiltration. *Journal of Clinical and Experimental Hematopathology* 63(3): 187-192, 2023.
 20. Shide K, Takenaka K, Kitanaka A, Numata A, Kamada T, Yamauchi T, Inagaki A, Mizuno S, Takami A, Ito S, Hagihara M, Usuki K, Maekawa T, Sunami K, Ueda Y, Tsutsui M, Ando M, Komatsu N, Ozawa K, Kurokawa M, Arai I, Mitani K, Akashi K, and Shimoda K. Nationwide prospective survey of secondary myelofibrosis in Japan: superiority of DIPSS-plus to MYSEC-PM as a survival risk model. *Blood Cancer Journal* 13(1): 110, 2023.
 21. Komeno Y, Uchiyama T, Kawano F, Kurihara Y, Kurokawa M, Ohara O, Kunishima S, and Ishiguro A. Inherited macrothrombocytopenia due to a novel splice donor site mutation of ITGB3. *Annals of Hematology* 102(10): 2947-2949, 2023.

Department of Allergy and Rheumatology

Professor

Keishi Fujio, M.D., Ph.D. (Rheumatology)

Associate Professor

Lecturer

Haruka Tsuchiya, M.D., Ph.D. (Rheumatology)

Hospital Lecturer

Yumi Tsuchida, M.D., Ph.D. (Rheumatology)

Toshihiko Komai, M.D., Ph.D. (Rheumatology)

Research Associate

Toshiaki Shimizu, M.D., Ph.D. (Allergology)

Masanori Kono, M.D., Ph.D. (Rheumatology)

Saeko Yamada, M.D., Ph.D. (Rheumatology)

Hideyuki Takahashi, M.D., Ph.D. (Rheumatology)

Nanami Mino, M.D., Ph.D. (Rheumatology)

Project professor

Tomohisa Okamura, M.D., Ph.D. (Rheumatology)

Project Research Associate

Takahiro Itamiya, M.D., Ph.D. (Rheumatology)

Manaka Goto, M.D., Ph.D. (Rheumatology)

Homepage <http://www.m.u-tokyo.ac.jp/mcm/>

Introduction and Organization

The Department of Allergy and Rheumatology presently consists of 12 staffs mentioned above, who preside over 2 medical staff, 18 graduate students for "Doctor of Medical Science". The outpatient facilities are situated on the 2nd floor of the Outpatient Clinic. The inpatient facility is mainly located on the 14th floor of the Hospital Ward A. The physician's office is situated in the West Hospital Ward and the research

rooms are located in the West Hospital Ward, the Molecular Life Innovation Ward, and the Clinical Research Center A.

Education

In regard to undergraduate education, the Department is in charge of internal medicine diagnosis and systemic lectures for M2 students and clinical lectures and bedside education for M3 and M4 students in

cooperation with other departments of internal medicine. The systemic lectures and clinical lectures cover clinical immunology, connective tissue diseases and allergy. Bedside education provides students with a good opportunity to learn patient care as well as practical knowledge through numerous seminars.

For postgraduate education, internal medicine trainees are accepted on rotation basis and trained as internist. Our department accepts students for "Doctor of Medical Science". Our 4-year education covers clinical immunology, molecular immunology, rheumatology and allergology.

Medical Care

General and special outpatient clinics are opened from Monday to Friday. Special outpatients clinics include clinics for rheumatoid arthritis, connective tissue diseases, bronchial asthma, allergy, and kidney disorders. For inpatients, there are presently 25 to 30 beds. Every week on Monday afternoon the charts are rounded and on Tuesday afternoon the professor makes his rounds. To achieve the highest quality of medical care, clinical conferences are held. Majority of patients in the ward are suffered from connective tissue diseases and usually exhibit multiple organ involvements. Therefore, a careful, well-rounded approach to each patient as a whole is required rather than a limited special approach to a single organ system.

Research

The Department consists of some laboratories in which clinical and basic studies are carried out concerning mainly rheumatology and allergology. Recently the mainstream of research has employed various techniques of molecular biology and cellular immunology. The principal research topics are listed below.

1. Functional genomics in autoimmune diseases, such as systemic lupus erythematosus, and its clinical application to precision medicine.
2. Analysis of newly identified autoimmune-associated T cell subset and its roles in autoimmune diseases.
3. Analysis of T cell and B cell repertoires in autoimmune diseases.
4. Analysis of synovial tissues in rheumatoid arthritis.
5. Analysis of mice models of immune-related diseases.
6. Analysis of autoimmune disease-specific iPS cells
7. Investigation of biomarkers in autoimmune disease.

Publications

1. Shoda H, Natsumoto B, Fujio K. Investigation of immune-related diseases using patient-derived induced pluripotent stem cells. *Inflamm Regen*. 2023;43(1):51.
2. Inoue M, Nagafuchi Y, Ota M, Tsuchiya H, Tateishi S, Kanda H, Fujio K. Carriers of HLA-DRB1*04:05 have a better clinical response to abatacept in rheumatoid arthritis. *Sci Rep*. 2023 Sep 14;13(1):15250.
3. Koda T, Natsumoto B, Shoda H, Fujio K. Nonepisodic Angioedema with Eosinophilia Following Receipt of the BNT162b2 mRNA COVID-19 Vaccine. *Intern Med*. 2023 Oct 15; 62(20):3063-3067.
4. Ota M, Nakano M, Nagafuchi Y, Kobayashi S, Hatano H, Yoshida R, Akutsu Y, Itamiya T, Ban N, Tsuchida Y, Shoda H, Yamamoto K, Ishigaki K, Okamura T, Fujio K. Multimodal repertoire analysis unveils B cell biology in immune-mediated diseases. *Ann Rheum Dis*. 2023 Nov; 82(11):1455-1463.
5. Jaccoud's Arthropathy in Systemic Lupus Erythematosus. Izuka S, Natsumoto B, Shoda H, Fujio K. **Intern Med**. 2023 Mar 1;62(5):809-810.
6. Yamada S, Nagafuchi Y, Fujio K. Pathophysiology and stratification of treatment-resistant rheumatoid arthritis. *Immunol Med*. 2024 Mar;47(1):12-23.
7. Kimura A, Takagi T, Thamamongood T, Sakamoto S, Ito T, Seki I, Okamoto M, Aono H, Serada S, Naka T, Imataka H, Miyake K, Ueda T, Miyanokoshi M, Wakasugi K, Iwamoto N, Ohmagari N, Iguchi T, Nitta T, Takayanagi H, Yamashita H, Kaneko H, Tsuchiya H, Fujio K, Handa H, Suzuki H. Extracellular aaRSs drive autoimmune and inflammatory responses in rheumatoid arthritis via the release of cytokines

- and PAD4. *Ann Rheum Dis.* 2023 Sep;82(9):1153-1161.
8. Nakajima S, Tsuchiya H, Ota M, Ogawa M, Yamada S, Yoshida R, Maeda J, Shirai H, Kasai T, Hirose J, Ninagawa K, Fujieda Y, Iwasaki T, Aizaki Y, Kajiyama H, Matsushita M, Kawakami E, Tamura N, Mimura T, Ohmura K, Morinobu A, Atsumi T, Tanaka Y, Takeuchi T, Tanaka S, Okamura T, Fujio K. Synovial Tissue Heterogeneity in Japanese Patients With Rheumatoid Arthritis Elucidated Using a Cell-Type Deconvolution Approach. *Arthritis Rheumatol.* 2023 Dec;75(12):2130-2136.
9. Natsumoto B, Shoda H, Nagafuchi Y, Ota M, Okumura T, Horie Y, Okamura T, Yamamoto K, Tsuji M, Otsu M, Taniguchi H, Fujio K. Functional evaluation of rare OASL variants by analysis of SLE patient-derived iPSCs. *J Autoimmun.* 2023 Sep;139:103085.
10. Nakagome K, Fujio K, Nagata M. Potential Effects of AIT on Nonspecific Allergic Immune Responses or Symptoms. *J Clin Med.* 2023 May 31;12(11):3776.
11. Suwa Y, Nagafuchi Y, Yamada S, Fujio K. The role of dendritic cells and their immunometabolism in rheumatoid arthritis. *Front Immunol.* 2023 May 12;14:1161148.
12. Isojima S, Yajima N, Yanai R, Miura Y, Fukuma S, Kaneko K, Fujio K, Oku K, Matsushita M, Miyamae T, Wada T, Tanaka Y, Kaneko Y, Nakajima A, Murashima A. Physician approval for pregnancy in patients with SLE showing only serological activity: A vignette survey study. *Mod Rheumatol.* 2023 May 27:road049.
13. Fujio K. Functional Genome Analysis for Immune Cells Provides Clues for Stratification of Systemic Lupus Erythematosus. *Biomolecules.* 2023 Mar 25;13(4):591.
14. Tsuchida Y, Shoda H, Sawada T, Fujio K. Role of autotaxin in systemic lupus erythematosus. *Front Med (Lausanne).* 2023 Apr 4;10:1166343.
15. Yoshitomi Y, Suwa Y, Tsuchiya H, Goto M, Natsumoto B, Shoda H, Fujio K. Pulmonary Hypertension Associated with Anti-synthetase Syndrome: A Case Report and Literature Review. *Intern Med.* 2023 Dec 15;62(24):3685-3689.
16. Nishiwaki A, Komai T, Nagafuchi Y, Tsuchida Y, Shoda H, Fujio K. Elevation of serum tenascin-C levels in dermatomyositis patients. *Int J Rheum Dis.* 2023 Aug;26(8):1635-1639.
17. Yamada S, Nagafuchi Y, Wang M, Ota M, Hatano H, Takeshima Y, Okubo M, Kobayashi S, Sugimori Y, Masahiro N, Yoshida R, Hanata N, Suwa Y, Tsuchida Y, Iwasaki Y, Sumitomo S, Kubo K, Shimane K, Setoguchi K, Azuma T, Kanda H, Shoda H, Zhang X, Yamamoto K, Ishigaki K, Okamura T, Fujio K. Immunomics analysis of rheumatoid arthritis identified precursor dendritic cells as a key cell subset of treatment resistance. *Ann Rheum Dis.* 2023 Jun; 82(6):809-819.
18. Tsuzuki S, Komai T, Nishiwaki A, Kamisawa T, Shoda H, Fujio K, Setoguchi K. Clinical features of IgG4-related disease with bronchial asthma. *Allergol Int.* 2023 Jul;72(3):484-487.
19. Matsuda KM, Kotani H, Yamaguchi K, Okumura T, Fukuda E, Kono M, Hisamoto T, Kawanabe R, Norimatsu Y, Kuzumi A, Fukayama M, Fukasawa T, Ebata S, Yoshizaki-Ogawa A, Okamura T, Shoda H, Fujio K, Goshima N, Sato S, Yoshizaki A. Significance of anti-transcobalamin receptor antibodies in cutaneous arteritis revealed by proteome-wide autoantibody screening. *J Autoimmun.* 2023 Feb;135:102995.
20. Sugimori Y, Iwasaki Y, Takeshima Y, Okubo M, Kobayashi S, Hatano H, Yamada S, Nakano M, Yoshida R, Ota M, Tsuchida Y, Nagafuchi Y, Shimane K, Yoshida K, Kurosaka D, Sumitomo S, Shoda H, Yamamoto K, Okamura T, Fujio K. Transcriptome Profiling of Immune Cell Types in Peripheral Blood Reveals Common and Specific Pathways Involved in the Pathogenesis of Myositis-Specific Antibody-Positive Inflammatory Myopathies. *ACR Open Rheumatol.* 2023 Feb;5(2):93-102.
21. Takahashi H, Komai T, Setoguchi K, Shoda H, Fujio K. A diagnostic score for eosinophilic granulomatosis with polyangiitis among eosinophilic disorders. *Allergol Int.* 2023 Apr; 72(2):316-323.
22. Izuka S, Komai T, Shoda H, Fujio K. Long-term risks of malignancy in myositis-specific antibody-positive idiopathic inflammatory

myopathy. *Rheumatol Int.* 2023 Feb;43(2):335-343.

Department of Infectious Diseases (Internal Medicine)

Professor

Takeya Tsutsumi, M.D., Ph.D.

Associate Professor

Shu Okugawa, M.D., Ph.D.

Assistant Professor

Mahoko Ikeda, M.D., Ph.D. Kazuhiko Ikeuchi, M.D., Ph.D. Shinya Yamamoto, M.D., Ph.D.

Homepage <https://plaza.umin.ac.jp/utid/index.html>

Introduction and Organization

The Department of Infectious Diseases has been one of the leading academic organizations specialized for internal medicine, in particular, infectious disease medicine in Japan since 1998, when the Departments of Internal Medicine, established in 1890, were rearranged into new ones according to subspecialty of internal medicine. Our department has been chiefly engaged in clinical, educational and research activities for infectious diseases including bacterial, fungal and viral infections of all organs including HIV infection, tuberculosis and viral hepatitis. Our department is located on 13th floor of the University of Tokyo Hospital Building and has well-furnished research laboratories including P-2 class laboratory, and computer rooms as own properties. In clinical and research activities, we are collaborating with the Department of Infection Control and Prevention. One professor, one associate professor, three assistant professors, some residents and full-time staff members are all performing their own duties in clinical, educational and research activities.

Clinical activities

We have hospital beds on the 13th floor of the Ward A of University of Tokyo Hospital. Diseases include HIV infection, viral hepatitis, pneumonia, drug-

resistant bacteria infections or tuberculosis, EBV infection, CMV infection, parasite infection, sexual transmitted infection, *etc.* Every effort is made to give patients the best care and best quality of life. Assistant associates and residents take care of inpatients. The case presentation by residents is held every day. Weekly clinical conference is held to discuss all cases, in particular, those with clinical problems difficult to be solved. Consultations are very frequent from other departments on the management of infectious diseases. The general diagnostic, therapeutic plans and decisions for each patient are given at the Professor's round.

Our department offers out-patient care everyday on infectious diseases and general medicine. We are also engaged in infection control and prevention of emerging infectious diseases with the department of infection control and prevention.

Teaching activities

Our department takes a part in clinical lectures and bed-side learning (clinical clerkship) of the internal medicine for undergraduate medical students according to the educational programs of the University of Tokyo. For the fourth year medical students, six lectures of infectious diseases are given. In addition, principles of medical diagnosis are taught at the bedside. During the clinical clerkship for fifth

and sixth year students, our associates teach them on man-to man basis the basic way of thinking for correct diagnosis and therapy, the techniques of interrogation and physical examination, the way for interpretations of laboratory tests and other medical examinations, and the basic medical procedures on each case. The education of junior residents and fellows is performed as described in “Clinical Activities”.

Research activities

Both clinical and basic research are necessary to improve the diagnosis and treatment to infectious diseases. The members of our department are doing best to obtain new findings using highly sophisticated methodologies. A intramural research conference is held, in which some members present their annual research progresses to be discussed by all the department staff. In addition, each laboratory holds its own conference and/or journal club on a weekly or bi-weekly basis.

The research field covers wide areas of infectious diseases including HIV infection, viral hepatitis and hepatocarcinogenesis, and bacterial infection. Also, various emerging and re-emerging infectious diseases are covered. Following themes are currently being investigated in the department.

- 1) Establishment of effective therapy for HCV and HBV infection: we have made a great contribution in the establishment of the guideline for treatment of hepatitis viral infection in Japan.
- 2) Establishment of effective therapy for HIV infection: we have made a great contribution in the establishment of the guideline for treatment of HIV infection in Japan.
- 3) Epidemiological study of infectious diseases by various pathogens.
- 4) Elucidation of the mechanism of hepatocarcinogenesis in hepatitis viral infection: the direct involvement of both HBV and HCV in hepatocarcinogenesis has been demonstrated using our transgenic mouse systems.
- 5) Pathogenesis of *Escherichia coli* infection.
- 6) Pathogenesis of *Clostridioides difficile* infection
- 7) Establishment of effective therapy for HCV/HIV co-infection: we have made a great contribution in the establishment of the guideline for treatment of

HCV/HIV co-infection in Japan.

- 8) Clinical research on COVID-19.

Publications

1. Ikeda M, Kobayashi T, Okugawa S, Fujimoto F, Okada Y, Tatsuno K, Higurashi Y, Tsutsumi T, Moriya K. Comparison of phylogenetic and virulence factors between *Escherichia coli* isolated from biliary tract infections and uropathogenic *Escherichia coli*. *Heliyon*. 2023; 9(11):e21748.
2. Ikeuchi K, Saito M, Adachi E, Koga M, Okushin K, Tsutsumi T, Yotsuyanagi H. Injection drug use and sexually transmitted infections among men who have sex with men: A retrospective cohort study at an HIV/AIDS referral hospital in Tokyo, 2013-2022. *Epidemiol Infect*. 2023;151:e195.
3. Uraki R, Ito M, Kiso M, Yamayoshi S, Iwatsuki-Horimoto K, Sakai-Tagawa Y, Imai M, Koga M, Yamamoto S, Adachi E, Saito M, Tsutsumi T, Otani A, Fukushi S, Watanabe S, Suzuki T, Kikuchi T, Yotsuyanagi H, Maeda K, Kawaoka Y. Antiviral efficacy against and replicative fitness of an XBB.1.9.1 clinical isolate. *iScience*. 2023;26(11):108147.
4. Kawase K, Okamoto K, Harada S, Nomura Y, Shimada S, Komae H, Kuroda R, Ideyama M, Soma K, Mizoguchi M, Higurashi Y, Ukai K, Adachi-Katayama M, Miwa T, Wakimoto Y, Oyabu T, Jubishi D, Hashimoto H, Okugawa S, Ono M, Doi K, Ushiku T, Tsutsumi T. A case of hypervirulent K1-ST23 *Klebsiella pneumoniae* endocarditis and papillary muscle rupture secondary to multiple site abscesses. *J Infect Chemother*. 2024;30(2):154-8.
5. Kado A, Tsutsumi T, Yotsuyanagi H, Ikeuchi K, Okushin K, Moriya K, Koike K, Fujishiro M. Noninvasive approach to indicate risk factors of nonalcoholic steatohepatitis overlapping autoimmune hepatitis based on peripheral lymphocyte pattern. *J Gastroenterol*. 2023;58(12):1237-51.
6. Adachi E, Saito M, Kikuchi T, Ikeuchi K, Koga M, Tsutsumi T, Yotsuyanagi H. Incidence of sexually transmitted hepatitis C virus infection among men who have sex with men in Japan

- from 2009 to 2023. *J Med Virol.* 2023;95(8):e29039.
7. Okushin K, Kurano M; UTH-UDCA Study Group; Yatomi Y, Moriya K, Fujishiro M, Tsutsumi T. Ursodeoxycholic acid for coronavirus disease 2019 prevention. *J Intern Med.* 2024;295(1):106-9.
 8. Yamamoto S, Yamayoshi S, Ito M, Sakai-Tagawa Y, Nakachi I, Baba R, Kamimoto S, Ogura T, Hagiwara S, Kato H, Nakajima H, Uwamino Y, Yagi K, Sugaya N, Nagai H, Saito M, Adachi E, Koga M, Tsutsumi T, Duong C, Okuda M, Murakami J, Furusawa Y, Ujie M, Iwatsuki-Horimoto K, Yotsuyanagi H, Kawaoka Y. Differences among epitopes recognized by neutralizing antibodies induced by SARS-CoV-2 infection or COVID-19 vaccination. *iScience.* 2023;26(7):107208.
 9. Ishizaka A, Koga M, Mizutani T, Uraki R, Yamayoshi S, Iwatsuki-Horimoto K, Yamamoto S, Imai M, Tsutsumi T, Suzuki Y, Kawaoka Y, Yotsuyanagi H. Research article antibody induction and immune response in nasal cavity by third dose of SARS-CoV-2 mRNA vaccination. *Virol J.* 2023;20(1):146.
 10. Okugawa S, Ikeda M, Kashiwabara K, Moritoyo T, Kohsaka T, Shimizu T, Hagiya H, Hasegawa K, Otsuka F, Miwa A, Kisimoto N, Mizoguchi A, Imamura A, Ikeuchi K, Tsutsumi T, Jubishi D, Hashimoto H, Okamoto K, Harada S, Inoue JI, Seto Y, Moriya K. Antiviral effect and safety of nafamostat mesilate in patients with mild early-onset COVID-19: An exploratory multicentre randomized controlled clinical trial. *Int J Antimicrob Agents.* 2023;62(3):106922.
 11. Okushin K, Yamana H, Tateishi R, Sato M, Tsutsumi T, Matsui H, Fushimi K, Yasunaga H, Koike K, Fujishiro M. Treatment and outcome of hepatorenal syndrome in Japan: a retrospective cohort study using a national inpatient database. *BMC Gastroenterol.* 2023;23(1):218.
 12. Uraki R, Ito M, Kiso M, Yamayoshi S, Iwatsuki-Horimoto K, Sakai-Tagawa Y, Imai M, Koga M, Yamamoto S, Adachi E, Saito M, Tsutsumi T, Otani A, Kashima Y, Kikuchi T, Theiler J, Yotsuyanagi H, Suzuki Y, Korber B, Kawaoka Y. Efficacy of antivirals and mRNA vaccination against an XBF clinical isolate. *Lancet Reg Health West Pac.* 2023;34:100777.
 13. Ikeuchi K, Tsutsumi T, Ishizaka A, Mizutani T, Sedohara A, Koga M, Tamaoki S, Yotsuyanagi H. Modulation of duodenal and jejunal microbiota by rifaximin in mice with CCl4-induced liver fibrosis. *Gut Pathog.* 2023;15(1):14.
 14. Yamaguchi R, Yamamoto T, Okamoto K, Harada S, Echizenya M, Tsutsumi T, Takada T. Teicoplanin and vancomycin as treatment for glycopeptide-susceptible *Enterococcus faecium* bacteraemia: a propensity score-adjusted non-inferior comparative study. *J Antimicrob Chemother.* 2023;78(5):1231-40.
 15. Bramer LM, Hontz RD, Einfeld AJ, Sims AC, Kim YM, Stratton KG, Nicora CD, Gritsenko MA, Schepmoes AA, Akasaka O, Koga M, Tsutsumi T, Nakamura M, Nakachi I, Baba R, Tateno H, Suzuki S, Nakajima H, Kato H, Ishida K, Ishii M, Uwamino Y, Mitamura K, Paurus VL, Nakayasu ES, Attah IK, Letizia AG, Waters KM, Metz TO, Corson K, Kawaoka Y, Gerbasi VR, Yotsuyanagi H, Iwatsuki-Horimoto K. Multi-omics of NET formation and correlations with CNDP1, PSPB, and L-cystine levels in severe and mild COVID-19 infections. *Heliyon.* 2023; 9(3):e13795.
 16. Uraki R, Ito M, Kiso M, Yamayoshi S, Iwatsuki-Horimoto K, Sakai-Tagawa Y, Furusawa Y, Imai M, Koga M, Yamamoto S, Adachi E, Saito M, Tsutsumi T, Otani A, Kashima Y, Kikuchi T, Yotsuyanagi H, Suzuki Y, Kawaoka Y. Efficacy of antivirals and bivalent mRNA vaccines against SARS-CoV-2 isolate CH.1.1. *Lancet Infect Dis.* 2023;23(5):525-6.
 17. Kado A, Inoue Y, Moriya K, Tsutsumi T, Ikeuchi K, Okushin K, Yotsuyanagi H, Koike K, Fujishiro M. Triglyceride level and soft drink consumption predict nonalcoholic fatty liver disease in nonobese male adolescents. *Hepatol Res.* 2023;53(6):497-510.
 18. Uraki R, Ito M, Kiso M, Yamayoshi S, Iwatsuki-Horimoto K, Furusawa Y, Sakai-Tagawa Y, Imai M, Koga M, Yamamoto S, Adachi E, Saito M, Tsutsumi T, Otani A, Kikuchi T, Yotsuyanagi H, Halfmann PJ, Pekosz A, Kawaoka Y. Antiviral and bivalent vaccine

- efficacy against an omicron XBB.1.5 isolate. *Lancet Infect Dis.* 2023;23(4):402-3.
19. Tanaka T, Koga M, Tsutsumi T, Hosaka T, Yotsuyanagi H. Some people living with HIV might need to pay attention to their mental health during the COVID-19 two years pandemic in Tokyo until the Omicron variant occur. *PCN Rep.* 2023;2(1):e73.
 20. Ikeda M, Okugawa S, Kashiwabara K, Moritoyo T, Kanno Y, Jubishi D, Hashimoto H, Okamoto K, Tsushima K, Uchida Y, Mitsumura T, Igari H, Tsutsumi T, Araoka H, Yatera K, Yamamoto Y, Nakamura Y, Otani A, Yamashita M, Wakimoto Y, Shinohara T, Adachi-Katayama M, Oyabu T, Kanematsu A, Harada S, Takeshita Y, Nakano Y, Miyazaki Y, Sakao S, Saito M, Ogura S, Yamasaki K, Kawasuji H, Hataji O, Inoue JI, Seto Y, Moriya K. Multicenter, single-blind, randomized controlled study of the efficacy and safety of favipiravir and nafamostat mesilate in patients with COVID-19 pneumonia. *Int J Infect Dis.* 2023;128:355-63.
 21. Uraki R, Ito M, Furusawa Y, Yamayoshi S, Iwatsuki-Horimoto K, Adachi E, Saito M, Koga M, Tsutsumi T, Yamamoto S, Otani A, Kiso M, Sakai-Tagawa Y, Ueki H, Yotsuyanagi H, Imai M, Kawaoka Y. Humoral immune evasion of the omicron subvariants BQ.1.1 and XBB. *Lancet Infect Dis.* 2023;23(1):30-2.
 22. Kingstad-Bakke B, Cleven T, Bussan H, Yount BL Jr, Uraki R, Iwatsuki-Horimoto K, Koga M, Yamamoto S, Yotsuyanagi H, Park H, Mishra JS, Kumar S, Baric RS, Halfmann PJ, Kawaoka Y, Suresh M. Airway surveillance and lung viral control by memory T cells induced by COVID-19 mRNA vaccine. *JCI Insight.* 2023;8(22):e172510.
 23. Ishii T, Hamada K, Jubishi D, Hashimoto H, Okamoto K, Hisasue N, Sunohara M, Saito M, Shinohara T, Yamashita M, Wakimoto Y, Otani A, Ikeda M, Harada S, Okugawa S, Moriya K, Yanagimoto S. Waning cellular immune responses and predictive factors in maintaining cellular immunity against SARS-CoV-2 six months after BNT162b2 mRNA vaccination. *Sci Rep.* 2023;13(1):9607.
 24. Oyama S, Adachi-Katayama M, Okamoto K, Jin C, Yamamura K, Saito Y, Kanematsu A, Otani A, Wakimoto Y, Oyabu T, Jubishi D, Hashimoto H, Harada S, Okugawa S, Moriya K. Preseptal cellulitis with *Streptococcus pyogenes* complicated by streptococcal toxic shock syndrome: A case report and review of literature. *J Infect Chemother.* 2023;29(8):783-6.
 25. Hashiba T, Sugahara M, Ota Y, Kaseda K, Kashiwagi Y, Nakamura M, Shinohara T, Ikeda M, Okugawa S, Sugimoto K, Sasaki K, Hamasaki Y, Yamada D, Kume H, Moriya K, Nangaku M. Paralytic Ileus during Treatment of Pulmonary and Renal Tuberculosis in a Non-Human Immunodeficiency Virus Patient: An Unusual Presentation of Tuberculosis-immune Reconstitution Inflammatory Syndrome. *Intern Med.* 2023; 62(17):2559-64.
 26. Ikeuchi K, Fukushima K, Tanaka M, Yajima K, Saito M, Imamura A. Changes in rapid plasma reagin titers in patients with syphilis before and after treatment: A retrospective cohort study in an HIV/AIDS referral hospital in Tokyo. *PLoS One.* 2023;18(9):e0292044.
 27. Adachi E, Ikeuchi K, Otani A, Saito M, Koga M, Yotsuyanagi H. Mpox associated with Pantone-Valentin leucocidin-producing methicillin-resistant *Staphylococcus aureus* among people with HIV. *J Infect Chemother.* 2023;29(7):710-2.
 28. Adachi E, Ikeuchi K, Koga M, Yotsuyanagi H. Background factors in people living with HIV in Japan who switch to cabotegravir plus rilpivirine: A pilot study. *J Infect Chemother.* 2023;29(1): 109-11.

Department of Stress Science and Psychosomatic Medicine

Associate Professor

Kazuhiro Yoshiuchi, M.D., Ph.D.

Project Assistant Professor

Tadahiro Yamazaki, M.D., Ph.D.

Assistant Professor

Nobuhiro Nohara, M.D.

Homepage <https://plaza.umin.ac.jp/~psmut/>

Introduction and Organization

The Department of Stress Science and Psychosomatic Medicine is one of 11 divisions of the Department of Internal Medicine, the University of Tokyo. It addresses eating disorders, panic disorder, and various psychosomatic diseases, including chronic headache, irritable bowel syndrome, functional dyspepsia, hypertension, diabetes mellitus, and hyperthyroidism. Our teaching staff comprises one associate professor, one project assistant professor, and one assistant professor. Other members include one senior resident, six graduate students. Our department was established in 1972 by Dr. Naka Ishikawa and Dr. Hiroyuki Suematsu at the University of Tokyo Hospital Branch. In October 2001, with the opening of the Inpatient Ward A, all clinical activities were centralized at the Hongo campus. In March 2002, following the relocation from the Branch Hospital, the department's offices and research laboratories were transferred to the Hongo Campus. As of 2023, the outpatient clinic is located on the second floor. The dedicated inpatient ward is situated on the 14th floor North of Inpatient Ward A. The department offices and research laboratories are housed on the second floor of the West Clinical Research Building.

Clinical activities

Our department oversees both the outpatient clinic and the inpatient ward. The ward is managed as part of the Division of General Internal Medicine, with senior residents, two assistant professors, and the associate professor providing practical guidance to senior and junior residents. The weekly professor's rounds are held on Thursday mornings. From April 2023 to March 2024, 2,548 patients, including 84 unique individuals, were admitted to the ward, most of whom were patients with eating disorders. The outpatient clinic operates every morning and afternoon. From April 2023 to March 2024, Our departments received 107 new outpatients with a total of 4,914 patients visits to date.

Educational activities

The lectures for fourth-year medical students consist of six sessions on psychosomatic medicine. Clinical clerkships and advanced clinical clerkships are offered to fifth-year medical students. Additionally, integrated clinical lectures on psycho-oncology are provided for fifth-year-medical students, while lectures on eating disorders are delivered to sixth-year-medical students. We aim to teach not only the fundamental knowledge of specific diseases, methods of physical examination, and interpretation of

laboratory data, but also clinical interviewing techniques, the development of doctor-patient relationships, and strategies for behavior modification.

For junior residents, our senior residents and assistant professors provide one-on-one instruction. Additionally, they receive guidance from our teaching staff on presenting the medical history of newly admitted patients during the weekly professor's rounds.

Research activities

Targeting stress-related diseases, including those covered by our department, lifestyle-related disease, and cancers, we are investigating their pathophysiology and psychopathology by analyzing bio-psycho-behavioral time-series data, various questionnaire responses, and autonomic nervous function. We are also actively conducting both basic and clinical research on substances related to eating behaviors.

Some representative research methods are as follows:

- 1) **Ecological Momentary Assessment (EMA):** Investigation of the neurobehavioral basis of stress-related diseases, such as tension-type headache, eating disorders, insomnia, and panic disorder, using portable devices for real-time assessment of subjective symptoms combined with ambulatory monitors, including electrocardiogram and actigraphy.
- 2) **Neuroendocrinological and Neuroimmunological Studies in Patients with Anorexia Nervosa:** Multidisciplinary investigations into energy metabolism during the refeeding phase; changes in various substances, such as neuropeptides, before and after treatment; relationship between bone metabolism and various makers; and exploration of biomarkers for evaluating treatment efficacy.
- 3) **Psycho-oncology:** Development of a new questionnaire for assessing depressive mood in cancer patients.

We are also collaborating with numerous scientists from other departments both in Japan and abroad. Monthly research conferences are held, during which one of the graduate students presents their research for

open discussion among all members of our department.

References

1. Matsuda Y, Tanimukai H, Inoue S, Hirayama T, Kanno Y, Kitaura Y, et al. A revision of JPOS/JASCC clinical guidelines for delirium in adult cancer patients: a summary of recommendation statements. *Jpn J Clin Oncol*. 2023; 53(9): 808-822.
2. Dhakal A, Kurisu K, Park S, Yoshiuchi K, Aoyagi Y. Association of psychosocial factors with physical activity among Japanese adults aged 65 and older: a 6-year repeated cross-sectional study from the Nakanojo Study. *Biopsychosoc Med*. 2023;17(1):32.
3. Kurisu K, Harashima S, Fujimori M, Akechi T, Yoshiuchi K, Uchitomi Y. Regional disparities in suicide among patients with cancer: A nationwide population-based study in Japan *Cancer Med*. 2023;12(19) 20052-20058.
4. Kurisu K, Nohara N, Inada S, Otani M, Noguchi H, Endo Y, et al. Economic costs for outpatient treatment of eating disorders in Japan. *J Eat Disord*. 2023;11(1):136.
5. Yamazaki T, Miyamoto S, Matsubara T, Yamagata H, Kobo H, Otani M, et al. Development of a Japanese Version of the Quality of Life at the End of Life-Cancer Scale. *J Pain Symptom Manage* 2023; 2023;66(2):e189-e195.
6. Yamanaka Y, Yoshiuchi K, Kubo C, Fukudo S, & Japanese Society of Psychosomatic Medicine. A nationwide questionnaire survey of physicians regarding the impact of the COVID-19 pandemic on patients and treatment system of psychosomatic medicine. *Biopsychosoc Med* 2023;17(1):21.
7. Nohara N, Yamanaka Y, Matsuoka M, Yamazaki T, Kawai K, Takakura S, et al. A multi-center, randomized, parallel-group study to compare the efficacy of enhanced cognitive behavior therapy (CBT-E) with treatment as usual (TAU) for anorexia nervosa: study protocol. *Biopsychosoc Med*. 2023;17(1):20.
8. Himmerich H, Lewis YD, Conti C, Mutwalli H,

- Karwautz A, Sjögren M, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines update 2023 on the pharmacological treatment of eating disorders. *The World Journal of Biological Psychiatry*. 2023;Apr 24:1-64.
9. Abe A, Fujisawa D, Miyajima K, Takeuchi E, Takeuchi M, Mimura M, et al. Influence of dosing pattern of antipsychotics on treatment outcome of delirium in patients with advanced cancer. *Jpn J Clin Oncol*. 2023;53(4):321-326.
 10. Kato A, Yoshiuchi K, Hashimoto H, Suzuki R, Yamauchi T, Kadowaki T. Feasibility, acceptability, and effects of a self-stigma reduction pilot program for Japanese individuals with type 2 diabetes. *PEC Innovation*. 2023;2: 100112.
 11. Kurisu K, Sato K, Matsuoka M, Otani M, Yoshiuchi K. Thrombocytopenia and PT-INR in patients with anorexia nervosa and severe liver dysfunction. *Biopsychosoc Med*. 2023;17(1):9.
 12. Kurisu K, Song YH, Yoshiuchi K. Developing action plans based on machine learning analysis to prevent sick leave in a manufacturing plant. *Journal of Occupational and Environmental Medicine*. 2023;65(2):140-145.

Internal Medicine

3. Clinical Laboratory Medicine and Pathology

Department of Transfusion Medicine

Professor

Hitoshi Okazaki, M.D., Ph.D.

Lecturer

Toshiyuki Ikeda, M.D., Ph.D.

Research Associate

Toshiya Hino, M.D., Ph.D., Naoyuki Shono, M.D., Ph.D.

Homepage <http://square.umin.ac.jp/traf-tky/>

Introduction and Organization

The Transfusion Medicine service was established in 1949, as an internal provisional measure, and officially established in 1966. In 1984, Professor Hiroshi Toyama assumed as the first Professor of the department. Professor Toyama greatly contributed to the field of transfusion medicine, especially by publishing “Transfusion Medicine” (actually in its 3rd edition), which is the bible of transfusion medicine in Japan. Other great contributions from the department are as follows. Dr. Kazuo Okochi, ex-lecturer of the department, is the pioneer in the field of transfusion-associated hepatitis research, ex-Professor Takeo Juji clarified the mechanisms of transfusion-associated graft-versus-host disease (TA-GVHD), a serious post-transfusion complication, and ex-Professor Yoichi Shibata contributed enormously to the field of platelet immunology. In 1997, the Department of Transfusion Medicine was established as a chair of the Division of Internal Medicine of the Graduate School of Medical Sciences, the University of Tokyo.

Actually, the department is composed of 6 medical doctors (4 full-time, and 2 partial-time), 10 laboratory technicians, 2-3 nurses and 1 office assistant.

Clinical activities

The main activity of the department of Transfusion

Medicine is the control, preservation, and provision of safe blood products and their derivatives (including albumin). The control of all blood products in the hospital is centralized to the department, which, in addition, provides information and orientation related to blood transfusion. Transfusion-related laboratory tests and tests for transfusion-transmitted infectious diseases are routine practices of the department, which also actively takes part in the diagnosis, prevention and treatment of adverse reactions and post-transfusion complications. Collection, preservation and provision of autologous blood are also important functions of the department, where the outpatient clinic for autologous blood was established by ex-Professor Koki Takahashi in January 2006. At the outpatient clinic, the first established in Japan, the transfusionist gives consultation to the patients, prepares the adequate blood collection schedule, takes the informed consent, and performs the blood collection, according to the surgeons' needs. Additionally, collection and preservation of peripheral blood stem cells are also performed.

The main activities are as follows:

- I Control and preservation of blood products and its derivatives;
- II. Laboratory tests
 - 1) Blood typing and histocompatibility testing;
 - 2) Detection of anti-erythrocyte, anti-leukocyte

- and anti-platelet antibodies;
- 3) Detection of HBV antigens and antibodies, HCV, HAV, HTLV and HIV antibodies;
- 4) HLA typing for hematopoietic stem cell transplantation and organ transplantation;

III. Clinical work

- 1) Pre-operative autologous blood collection and preservation;
- 2) Collection and preservation of peripheral blood stem cells for transplantation;

Teaching activities

Sixth-grade medical students are provided with practical courses focusing on clinical practice of blood transfusion and laboratory tests. Courses are given in small groups of 6 students each, in a total of 18 groups per year. The course lasts 5 days/week, including the following subjects;

- 1) Visit to the laboratories of the department to understand the routine of a laboratory;
- 2) Introduction to the blood group types (red cells, platelets, leukocytes) and their importance in transfusion medicine and in transplantation (bone marrow and organ);
- 3) Methodology of blood typing and compatibility testing for transfusion;
- 4) Methodology for screening of irregular antibodies, and their importance in transfusion practice;
- 5) Introduction to the post-transfusional complications, their etiology, prevention and treatment.
- 6) Introduction to the preventive measures of blood borne viral transmission, especially focusing on the NAT test and the look-back survey.
- 7) Acquisition of informed consents related to blood transfusion, using the role playing method.
- 8) The indications and techniques of autologous blood collection and preservation;
- 9) The techniques for peripheral blood stem cells (PBSCs) collection and preservation, as well as their clinical application;
- 10) The recent advances in the field of blood transfusion, including the “Blood Law”, and the recently revised “Indications of blood products” and “The principles of transfusion practice”.
- 11) One-day visit to the Japanese Red Cross Blood Center, to learn the general process of blood

donation and transfusion, including the types of blood products, and their indications.

Research activities

Research on red cells, leukocytes, and platelets, the post-transfusional complications, transplantation immunology, immunotherapy, and stem cell biology are the main themes of the department. Typing of blood cells is performed by serological and DNA-based methods. The HLA typing, which was introduced by ex-Professor Takeo Juji, one of the pioneers of this field, is an essential test for hematopoietic stem cell and organ transplantations, and still continues as one of the most important research fields of the department. The mixed-passive hemagglutination (MPHA) method, the most popular methodology for platelet serology in Japan, was developed by ex-Professor Yoichi Shibata and its applicability is now extended for granulocyte as well as endothelial cell serology. Transplantation immunology, including stem cell biology is also an important subject. Also, development of new materials for medical use is also being researched. Recently, the risk factors of the detrimental effects of autologous blood donation, especially focusing on the noninvasive measurement of circulating blood volume, are being investigated. Following are the main themes.

- 1. Detection of platelet alloantigens and antibodies and their role in the transfusion practice.
- 2. Diagnosis and prevention of post-transfusional complications and thrombocytopenic purpura of the newborn.
- 3. Clinical application of refrigerated and frozen-stored blood for autologous transfusion in surgical patients, and the improvement of the preservation methods.
- 4. Study on the effect of pre-storage leukoreduction of autologous blood for the prevention of possible adverse effects.
- 5. Development of a new methodology for platelet cross-match.
- 6. HLA and HPA genotyping.
- 7. Development of a new methodology for evaluation of platelet function.
- 8. Ex-vivo expansion of hematopoietic stem cells and their clinical application.

9. Pathophysiology of TRALI and TACO.
10. Study on the risk factors of autologous blood donation.
11. Study on the correlation between the results obtained by conventional coagulation tests and the measurement results of thromboelastograms.

Reproductive, Developmental and Aging Sciences

1. Obstetrics and Gynecology

Department of Reproductive Endocrinology

Professors

Yutaka Osuga

Assistant Professors

Miyuki Harada

Homepage http://www.h.u-tokyo.ac.jp/patient/depts/a_joseika02/index.html
[#reproduction](#)
<https://www.gynecology-htu.jp/>

Organization

The Department of Reproductive Endocrinology is organized by Assistant Professors Takeshi Nagamatsu. All the staff members are taking part in both clinical and research activities. For the clinical aspect, we are engaged with in-patient and out-patient care including the activities in the delivery units.

Activities

In clinical section, we have an out-patient clinic for infertility, gynecological endocrine diseases, genetic counseling and assisted reproductive technologies (ART).

We have a highly organized infertility clinic, where every patient is systemically examined and after diagnosis of underlying infertility factor (s) appropriate treatment is performed following our protocol. Once it turns out that higher level of treatment is necessary, ART is applied to such cases. We have been engaged in *in vitro* fertilization and embryo transfer (IVF-ET) as a main axis of ART for twenty years. Conventional IVF-ET is mainly indicated to cases with tubal factor, mild male factor, immunological factor or of unexplained infertility factor. In case of severe male factor or other fertilization disorder intracytoplasmic sperm injection (ICSI) is performed. Now we have about 220 OPU cycles of IVF-ET every year, which

conventional IVF-ET and ICSI share almost equally. The clinical pregnancy rate of conventional IVF-ET is around 30% per embryo transfer cycle, which is comparable with that of ICSI. Other ART techniques such as embryo cryopreservation and assisted hatching are also performed.

In basic research section, a couple of projects as follows are under way, some of which have already yielded interesting findings; 1) the mechanism of folliculogenesis and follicular apoptosis in the ovary, 2) the functions of gynecologic hormones such as gonadotropins and ovarian steroids, 3) the analysis / etiology of endometriosis, adenomyosis and fibroma and so on.

References published in 2023

1. Katagiri Y, Jwa SC, Kuwahara A, Iwasa T, Ono M, Kato K, Kishi H, Kuwabara Y, Harada M, Hamatani T, Osuga Y. Assisted reproductive technology in Japan: A summary report for 2020 by the ethics Committee of the Japan Society of obstetrics and gynecology. *Reprod Med Biol*. 2023 Jan 4;22(1):e12494.
2. Hiratsuka D, Aikawa S, Hirota Y, Fukui Y, Akaeda S, Hiraoka T, Matsuo M, Osuga Y. DNA Methylation and Histone Modification Are the Possible Regulators of Preimplantation Blastocyst Activation in Mice. *Reprod Sci*. 2023

- Feb;30(2):494-525.
3. Koike H, Harada M, Kusamoto A, Xu Z, Tanaka T, Sakaguchi N, Kunitomi C, Azhary JMK, Takahashi N, Urata Y, Osuga Y. Roles of endoplasmic reticulum stress in the pathophysiology of polycystic ovary syndrome. *Front Endocrinol (Lausanne)*. 2023 Feb 15;14:1124405.
4. Osuga Y, Shirasu K, Tsushima R, Ishitani K. Short-term efficacy and safety of early medical abortion in Japan: A multicenter prospective study. *Reprod Med Biol*. 2023 Mar 31;22(1):e12512.
5. Akashi K, Yamada M, Jwa SC, Utsuno H, Kamijo S, Hirota Y, Tanaka M, Osuga Y, Kuji N. Artificial oocyte activation using Ca^{2+} ionophores following intracytoplasmic sperm injection for low fertilization rate. *Front Endocrinol (Lausanne)*. 2023 Mar 9;14:1131808.
6. Ishizawa C, Hirota Y, Iida R, Kaku T, Hirata T, Fukui Y, Omura E, Akaeda S, Hiraoka T, Matsuo M, Osuga Y. Levonorgestrel-Releasing Intrauterine System Improves Menorrhagia-Related Quality of Life in Patients with Symptomatic Adenomyosis. *Reprod Sci*. 2023 Mar;30(3):966-973.
7. Salehi R, Wyse BA, Asare-Werehene M, Esfandiarinezhad F, Abedini A, Pan B, Urata Y, Gutsol A, Vinas JL, Jahangiri S, Xue K, Xue Y, Burns KD, Vanderhyden B, Li J, Osuga Y, Burger D, Tan SL, Librach CL, Tsang BK. Androgen-induced exosomal miR-379-5p release determines granulosa cell fate: cellular mechanism involved in polycystic ovaries. *J Ovarian Res*. 2023 Apr 12;16(1):74.
8. Mitake S, Wada-Hiraike O, Kashiwabara K, Nakamura A, Nasu R, Hine M, Matsuyama Y, Fujii T, Osuga Y. Distribution of the follicular and luteal phase lengths and their age-dependent changes in Japanese women: A large population study. *Reprod Med Biol*. 2023 May 12;22(1):e12516.
9. Fukui Y, Hirota Y, Aikawa S, Sakashita A, Shimizu-Hirota R, Takeda N, Ishizawa C, Iida R, Kaku T, Hirata T, Hiraoka T, Akaeda S, Matsuo M, Osuga Y. The EZH2-PRC2-H3K27me3 axis governs the endometrial cell cycle and differentiation for blastocyst invasion. *Death Dis*. 2023 May 18;14(5):320.
10. Chiba Y, Nose-Ogura S, Sekiguchi K, Eda K, Nakamura H, Koshimizu T, Yamamoto H, Yamaguchi T, Harada M, Wada-Hiraike O, Osuga Y. Development of University of Tokyo's eating disorders inventory in female athletes. *J Obstet Gynaecol Res*. 2023 Jul;49(7):1854-1866.
11. Urata Y, Salehi R, Wyse BA, Jahangiri S, Librach CL, Tzeng CR, Osuga Y, Tsang B. Neuropeptide Y directly reduced apoptosis of granulosa cells, and the expression of NPY and its receptors in PCOS subjects. *J Ovarian Res*. 2023 Aug 31;16(1):182.
12. Hisano M, Nakagawa K, Ono M, Yoshino O, Saito T, Hirota Y, Inoue E, Kikuchi K, Nakamura H, Yamaguchi K. Multicenter, 2-dose single-group controlled trial of tacrolimus for the severe infertility patients. *Medicine (Baltimore)*. 2023 Aug 11;102(32):e34317.
13. Hiratsuka D, Omura E, Ishizawa C, Iida R, Fukui Y, Hiraoka T, Akaeda S, Matsuo M, Harada M, Wada-Hiraike O, Osuga Y, Hirota Y. Pregnancy is associated with reduced progression of symptomatic adenomyosis: a retrospective pilot study. *BMC Pregnancy Childbirth*. 2023 Sep 4;23(1):634.
14. Ono M, Harada M, Horie A, Dai Y, Horiguchi I, Kikuchi E, Kimura F, Koizumi T, Komeya M, Mizunuma N, Oseto K, Ota K, Shimizu C, Sugimoto K, Takae S, Takeuchi E, Nishi H, Yumura Y, Furui T, Takai Y, Morishige KI, Watanabe C, Osuga Y, Suzuki N. Effect of a web-based fertility preservation training program for medical professionals in Japan. *Int J Clin Oncol*. 2023 Sep;28(9):1112-1120.
15. Hiraoka T, Osuga Y, Hirota Y. Current perspectives on endometrial receptivity: A comprehensive overview of etiology and treatment. *J Obstet Gynaecol Res*. 2023 Oct;49(10):2397-2409.
16. Harada S, Yamada M, Shirasawa H, Jwa SC, Kuroda K, Harada M, Osuga Y. Fact-finding survey on assisted reproductive technology in Japan. *J Obstet Gynaecol Res*. 2023 Nov;49(11):2593-2601.
17. Takeshige Y, Jwa SC, Hirota Y, Osuga Y, Kuramoto T, Mio Y, Furui K, Kinutani M,

- Shiotani M, Asada Y, Kamiya H, Yoshida H, Igarashi H, Kyono K. Clinical outcomes of personalized blastocyst embryo transfer after endometrial receptivity analysis: A multicenter, retrospective cohort study. *Reprod Med Biol.* 2023 Nov 29;22(1):e12550.
18. Katagiri Y, Jwa SC, Kuwahara A, Iwasa T, On M, Kato K, Kishi H, Kuwabara Y, Taniguchi F, Harada M, Iwase A, Osuga Y. Assisted reproductive technology in Japan: A summary report for 2021 by the Ethics Committee of the Japan Society of Obstetrics and Gynecology. *Reprod Med Biol.* 2023 Dec 30;23(1):e12552.
19. Xu Z, Takahashi N, Harada M, Kunitomi C, Kusamoto A, Koike H, Tanaka T, Sakaguchi N, Urata Y, Wada-Hiraike O, Hirota Y, Osuga Y. The Role of Cellular Senescence in Cyclophosphamide-Induced Primary Ovarian Insufficiency. *Int J Mol Sci.* 2023 Dec 6;24(24):17193.

Department of Gynecologic Oncology

Professor

Yutaka Osuga,

Assistant Professor

Kenbun Sone

Homepage <https://www.gynecology-htu.jp/>

Organization

The Department of Gynecologic Oncology is organized by one professor and one associate professors, being directed practically by Professor Yutaka Osuga, the Department of Obstetrics and Gynecology. The staff members are taking part in clinical and research activities as well as teaching activities.

Activities

In the clinical activities, more than 150 patients with gynecological cancer and more than one thousand patients with benign gynecological diseases are treated in our department every year. Appropriate combinations of surgical treatment, chemotherapy and radiotherapy have been chosen according to the patients' conditions, and favorable clinical outcomes have been achieved. Minimally-invasive surgery is frequently employed in the treatment of benign and gynecological tumors and genital organ malformation. We take charge of more than 400 cases of endoscopic gynecological surgery including robotically-assisted laparoscopic surgery annually. We also employ the clinical trials of JCOG (Japan Clinical Oncology Group) and JGOG (Japanese Gynecologic Oncology Group) as well as the single-institution clinical trials. Advanced treatment performed in our department is as follows:

- (1) Cancer genomic medicine (Genetic tests of the hereditary gynecologic cancers)

- (2) Radical trachelectomy for women of childbearing age with early cervical cancer
- (3) Laparoscopic para-aortic lymphadenectomy for endometrial cancer
- (4) Laparoscopic sacralcolpopexy for pelvic organ prolapse
- (5) Adenomyomectomy

Based on our knowledge and experience in this field, we also perform clinical, translational and basic research energetically. Our department focuses on the pathogenesis and the pathophysiology of malignant gynecological diseases such as cervical, endometrial and ovarian cancers, and benign diseases such as endometriosis and adenomyosis. Our ongoing projects are as follows:

- (1) Establishment of new therapeutic approach targeting histone modification enzymes in gynecological malignancies
- (2) Search for epigenomic biomarkers using deep learning in gynecological malignancies
- (3) Development of an automated hysteroscopic diagnosis system for gynecological diseases using deep learning
- (4) Control mechanism of genome stability in gynecological malignancies
- (5) Search for novel biomarkers using germline and somatic variants in gynecological cancers
- (6) Genomic approach to elucidate the pathogenesis and pathophysiology of endometriosis and adenomyosis

- (7) Immunological aspects in the pathophysiology of endometriosis

References published in 2023

1. High-Throughput Functional Evaluation of MAP2K1 Variants in Cancer. Mizuno S, Ikegami M, Koyama T, Sunami K, Ogata D, Kage H, Yanagaki M, Ikeuchi H, Ueno T, Tanikawa M, Oda K, Osuga Y, Mano H, Kohsaka S. *Mol Cancer Ther.* 2023 Feb 1;22(2):227-239.
2. Effect of pelvic radiotherapy on patients with stage IB-IIA cervical cancer after radical hysterectomy: A single-center retrospective study. Ishizawa C, Taguchi A, Tanikawa M, Honjo H, Nishijima A, Eguchi S, Miyamoto Y, Sone K, Tsuruga T, Mori M, Osuga Y. *Oncol Lett.* 2023 Feb 2;25(3):112.
3. Cells with stem-like properties are associated with the development of HPV18-positive cervical cancer. Kusakabe M, Taguchi A, Tanikawa M, Wagatsuma R, Yamazaki M, Tsuchimochi S, Toyohara Y, Kawata A, Baba S, Ueno T, Sone K, Mori-Uchino M, Ikemura M, Matsunaga H, Nagamatsu T, Wada-Hiraike O, Kawazu M, Ushiku T, Takeyama H, Oda K, Kawana K, Mano H, Osuga Y. *Cancer Sci.* 2023 Mar;114(3):885-895.
4. Efficacy of regional cooling + oral dexamethasone for primary prevention of hand-foot syndrome associated with pegylated liposomal doxorubicin. Nara K, Taguchi A, Yamamoto T, Tsuruga T, Tojima Y, Miyamoto Y, Tanikawa M, Sone K, Mori M, Takada T, Suzuki H, Osuga Y. *Support Care Cancer.* 2023 Apr 19;31(5):283.
5. Application of organoid culture from HPV18-positive small cell carcinoma of the uterine cervix for precision medicine. Kusakabe M, Taguchi A, Tanikawa M, Hoshi D, Tsuchimochi S, Qian X, Toyohara Y, Kawata A, Wagatsuma R, Yamaguchi K, Yamamoto Y, Ikemura M, Sone K, Mori-Uchino M, Matsunaga H, Tsuruga T, Nagamatsu T, Kukimoto I, Wada-Hiraike O, Kawazu M, Ushiku T, Takeyama H, Oda K, Kawana K, Hippo Y, Osuga Y. *Cancer Med.* 2023 Apr;12(7):8476-8489.
6. A case of refractory pelvic squamous cell carcinoma of unknown primary that responded to nivolumab. Komura A, Taguchi A, Ikemura M, Nishijima A, Miyamoto Y, Tanikawa M, Sone K, Mori M, Oda K, Osuga Y. *J Obstet Gynaecol Res.* 2023 Apr;49(4):1300-1304.
7. Evolution of a surgical system using deep learning in minimally invasive surgery (Review). Sone K, Tanimoto S, Toyohara Y, Taguchi A, Miyamoto Y, Mori M, Iriyama T, Wada-Hiraike O, Osuga Y. *Biomed Rep.* 2023 May 30;19(1):45.
8. Carcinogenesis and management of human papillomavirus-associated cervical cancer. Kusakabe M, Taguchi A, Sone K, Mori M, Osuga Y. *Int J Clin Oncol.* 2023 Aug;28(8):965-974.
9. Heterogeneous effects of cytotoxic chemotherapies for platinum-resistant ovarian cancer. Nara K, Taguchi A, Yamamoto T, Hara K, Tojima Y, Honjoh H, Nishijima A, Eguchi S, Miyamoto Y, Sone K, Mori M, Takada T, Osuga Y. *Int J Clin Oncol.* 2023 Sep;28(9):1207-1217.
10. Cancer of unknown primary histologically, genetically and spatially diagnosed as left ovary-derived cancer: A case report. Honjoh H, Taguchi A, Rokutan H, Mori A, Ando T, Nishijima A, Eguchi S, Miyamoto Y, Sone K, Uchino-Mori M, Osuga Y. *Oncol Lett.* 2023 Oct 19;26(6):522.
11. Prognosis of patients with endometrial cancer or atypical endometrial hyperplasia after complete remission with fertility-sparing therapy. Ga H, Taguchi A, Honjoh H, Nishijima A, Eguchi S, Miyamoto Y, Sone K, Mori M, Osuga Y. *Arch Gynecol Obstet.* 2023 Nov;308(5):1629-1634.
12. Characterization of a fluorescence imaging probe that exploits metabolic dependency of ovarian clear cell carcinoma. Tsuchimochi S, Wada-Hiraike O, Urano Y, Kukita A, Yamaguchi K, Honjo H, Taguchi A, Tanikawa M, Sone K, Mori-Uchino M, Tsuruga T, Oda K, Osuga Y. *Sci Rep.* 2023 Nov 20;13(1):20292.
13. Risk stratification of invasive cervical cancer diagnosed after cervical conization. Shiga T, Taguchi A, Mori M, Yamaguchi S, Honjoh H, Nishijima A, Eguchi S, Miyamoto Y, Sone K, Kawana K, Osuga Y. *Jpn J Clin Oncol.* 2023 Dec 7;53(12):1138-1143.

Department of Perinatal Medicine

Professor

Osuga Yutaka

Assistant Professor

Takayuki Iriyama

Homepage <https://www.obstetrics-htu.jp/english/>

Organization

The Department of Perinatal Medicine is organized by one professor and one associate professor, being directed practically by Professor Tomoyuki Fujii, the chairman of the Department of Obstetrics and Gynecology. All the staff members take part in both clinical and research activities, as well as teaching activities, with about 20 associates of the University of Tokyo Hospital. From the clinical aspect, they are engaged with in-patient and out-patient care including the activities in the delivery units.

Activities

Clinical service for perinatology in the University of Tokyo Hospital consists of out-patient clinic and the delivery unit. [See Delivery Unit of the University of Tokyo Hospital]

With the advance of the techniques for prenatal diagnosis of pathological pregnancies and congenital malformations, the area of fetal medicine is spreading. Intensive scrutiny using ultrasonography makes it possible to clarify background causes of fetal growth restriction. New techniques for genetic analysis have been introduced into prenatal diagnosis. The perinatologists and medical engineering team in our department are working on clinical research to clarify the pathoetiology of preterm birth and preeclampsia. Perineal ultrasound is a new approach for assessing labor progress. Using this technique, our challenge is to establish novel clinical approach for precise and objective evaluation of labor progression which can contribute to safer labor management. Pregnancy

complicated with adenomyosis is associated with variety of adverse perinatal events, such as second trimester miscarriage, preeclampsia, and placental malposition. Our mission is to establish optimal clinical management which improves perinatal outcomes for both the mother and the neonate.

Recurrent pregnancy loss (RPL) is a condition in which a woman has two or more clinical pregnancy losses. Our department has been providing a “special clinic for RPL”. About 150 new couples with RPL visit us every year. Underlying causes of RPL are identified by screening tests. Anatomical, chromosomal, hormonal, biological, and autoimmune factors can trigger RPL. For RPL women with autoimmune factors, especially with antiphospholipid antibodies, anti-coagulation therapy using heparin and low dose aspirin is performed. For low risk group, low dose aspirin is administered. Causative factor is not detectable in half of the women with RPL. Supportive care rather than pharmacological intervention is important for those women. In our clinic, mental stress in RPL women is evaluated using K6 scale. We are investigating the relationship between their mental status and the outcome in the subsequent pregnancy.

After a renewal of the inpatient's wards for obstetrics and NICU/GCU/PICU in 2019, the new perinatal medical center restarted as one of the largest facility in Japan and is accommodated with full capacity to treat with all maternal and fetal diseases. We are proud to provide advanced medical care for every patient.

References published in 2023

1. Toshimitsu M, Iriyama T, Sato J, Abe O, Ichinose M, Sayama S, et al. A Case of Ruptured Exophytic Uterine Artery Pseudoaneurysm without Specific Risk Factors That Manifested Seven Days after Vaginal Delivery. *Case Rep Obstet Gynecol.* 2023;2023:1637463.
2. Yano E, Iriyama T, Sayama S, Ariyosi Y, Akiba N, Ichinose M, et al. The head direction to the angle of progression ratio: a quantitative parameter for intrapartum evaluation of cephalic malposition. *Am J Obstet Gynecol MFM.* 2023;5(1):100755.
3. Yanagisawa M, Nagamatsu T, Kurano M, Misumi F, Taguchi A, Akiba N, et al. Upregulation of autotaxin by oxidative stress via Nrf2 activation: A novel insight into the compensation mechanism in preeclamptic placenta. *J Reprod Immunol.* 2023;160:104153.
4. Suzuki K, Fujii T, Iriyama T, Sato Y, Kawasaki T, Hayashi K, et al. [Optimal safety management procedures for medications with potent teratogenic properties: a prospective intervention cluster randomized non-inferiority comparative study]. *Rinsho Ketsueki.* 2023;64(3):175-86.
5. Sayama S, Iriyama T, Takeiri Y, Hashimoto A, Toshimitsu M, Ichinose M, et al. Clinical characteristics and outcomes of women with adenomyosis pain during pregnancy: a retrospective study. *J Perinat Med.* 2024;52(2):186-91.
6. Sayama S, Iriyama T, Hashimoto A, Suzuki K, Ariyoshi Y, Yano E, et al. Possible risks and benefits of adenomyomectomy on pregnancy outcomes: a retrospective analysis. *AJOG Glob Rep.* 2023;3(4):100265.
7. Nakajima K, Fujii T, Iriyama T, Ichinose M, Toshimitsu M, Sayama S, et al. Efficacy of prompt administration of cryoprecipitate in severe postpartum hemorrhage of preeclampsia patients. *J Obstet Gynaecol Res.* 2023;49(12):2811-6.
8. Miyatake R, Fujii T, Kumasawa K, Ichinose M, Toshimitsu M, Sayama S, et al. The sFlt-1/PIGF Ratio Trend Is Useful in Predicting Preeclampsia Severity in Hyperreactio Luteinalis Complicated with Preeclampsia. *Case Rep Obstet Gynecol.* 2023;2023:7352947.
9. Miyashita D, Sayama S, Iriyama T, Nakazaki K, Toshimitsu M, Seyama T, et al. A successful management of refractory immune thrombocytopenic purpura with Eltrombopag during pregnancy complicated with superimposed preeclampsia. *Oxf Med Case Reports.* 2023;2023(5):omad047.
10. Kato K, Nagamatsu T, Yamaguchi S, Ichinose M, Sayama S, Toshimitsu M, et al. Changes in fetal presentation in the preterm period and the prediction of non-cephalic delivery. *J Matern Fetal Neonatal Med.* 2023;36(1):2141564.
11. Kato K, Iriyama T, Hara K, Suzuki K, Hashimoto A, Sayama S, et al. Increased risk of placenta previa and preterm birth in pregnant women with endometriosis/adenomyosis: A propensity-score matching analysis of a nationwide perinatal database in Japan. *J Obstet Gynaecol Res.* 2024;50(3):351-7.
12. Hashimoto A, Iriyama T, Sayama S, Okamura A, Kato K, Fujii T, et al. Differences in the incidence of obstetric complications depending on the extent and location of adenomyosis lesions. *J Matern Fetal Neonatal Med.* 2023;36(2):2226789.

Department of Molecular and Cellular Reproductive Medicine

Professor

Yutaka Osuga

Associate Professor

Osamu Hiraiki

Homepage <https://www.gynecology-htu.jp/>

Organization

The Department of Molecular and Cellular Reproductive Medicine is organized by one professor and one associate professor.

Activities

Our department mainly aims to investigate the reproductive endocrinology, and molecular biological methods are utilized to accomplish this purpose. Basic researches are currently performed and we report many interesting findings annually. We specifically focus on the role of inflammation and transcription machinery in these issues. Senescence and aging process are also extensively investigated.

- 1) The mechanism of folliculogenesis, follicular atresia and intrafollicular microenvironment in the ovary.
- 2) The physiological functions of sex steroid hormones and gonadotropins.
- 3) The molecular mechanisms of endometriosis.
- 4) The molecular mechanisms of uterine fibroid and adenomyosis.
- 5) The effects of aging and cellular senescence on the reproductive system.

In clinical section, we have an out-patient clinic for infertility, gynecological endocrine disorders and genetic counseling. We also perform minimally invasive surgery for benign gynecological diseases including endometriosis, uterine fibroid, adenomyosis,

infertility, and pelvic organ prolapse. More than 90% of surgery cases for benign gynecological disorders are operated using endoscope, and we deal with more than 400 cases annually.

In accordance with the notion of life stage specific approaches, we also manage patients complaining primary/secondary amenorrhea, infertility, dysmenorrhea, heavy menstrual bleeding, and climacterium. Osteoporosis in their 10's to 20's and perimenopausal age could be a heavy burden for patients and we have already established the primary care system for these women. Numerous number of female athletes refer to our clinic as well.

References published in 2023

1. Katagiri Y, Jwa SC, Kuwahara A, Iwasa T, Ono M, Kato K, Kishi H, Kuwabara Y, Harada M, Hamatani T, Osuga Y. Assisted reproductive technology in Japan: A summary report for 2020 by the ethics Committee of the Japan Society of obstetrics and gynecology. *Reprod Med Biol.* 2023 Jan 4;22(1):e12494.
2. Hiratsuka D, Aikawa S, Hirota Y, Fukui Y, Akaeda S, Hiraoka T, Matsuo M, Osuga Y. DNA Methylation and Histone Modification Are the Possible Regulators of Preimplantation Blastocyst Activation in Mice. *Reprod Sci.* 2023 Feb;30(2): 494-525.
3. Koike H, Harada M, Kusamoto A, Xu Z, Tanaka T, Sakaguchi N, Kunitomi C, Azhary JMK,

- Takahashi N, Urata Y, Osuga Y. Roles of endoplasmic reticulum stress in the pathophysiology of polycystic ovary syndrome. *Front Endocrinol (Lausanne)*. 2023 Feb 15;14:1124405.
4. Osuga Y, Shirasu K, Tsushima R, Ishitani K. Short-term efficacy and safety of early medical abortion in Japan: A multicenter prospective study. *Reprod Med Biol*. 2023 Mar 31;22(1):e12512.
 5. Akashi K, Yamada M, Jwa SC, Utsuno H, Kamijo S, Hirota Y, Tanaka M, Osuga Y, Kuji N. Artificial oocyte activation using Ca²⁺ ionophores following intracytoplasmic sperm injection for low fertilization rate. *Front Endocrinol (Lausanne)*. 2023 Mar 9;14:1131808.
 6. Ishizawa C, Hirota Y, Iida R, Kaku T, Hirata T, Fukui Y, Omura E, Akaeda S, Hiraoka T, Matsuo M, Osuga Y. Levonorgestrel-Releasing Intrauterine System Improves Menorrhagia-Related Quality of Life in Patients with Symptomatic Adenomyosis. *Reprod Sci*. 2023 Mar;30(3):966-973.
 7. Salehi R, Wyse BA, Asare-Werehene M, Esfandiari-Nezhad F, Abedini A, Pan B, Urata Y, Gutsol A, Vinas JL, Jahangiri S, Xue K, Xue Y, Burns KD, Vanderhyden B, Li J, Osuga Y, Burger D, Tan SL, Librach CL, Tsang BK. Androgen-induced exosomal miR-379-5p release determines granulosa cell fate: cellular mechanism involved in polycystic ovaries. *J Ovarian Res*. 2023 Apr 12;16(1):74.
 8. Mitake S, Wada-Hiraike O, Kashiwabara K, Nakamura A, Nasu R, Hine M, Matsuyama Y, Fujii T, Osuga Y. Distribution of the follicular and luteal phase lengths and their age-dependent changes in Japanese women: A large population study. *Reprod Med Biol*. 2023 May 12;22(1):e12516.
 9. Fukui Y, Hirota Y, Aikawa S, Sakashita A, Shimizu-Hirota R, Takeda N, Ishizawa C, Iida R, Kaku T, Hirata T, Hiraoka T, Akaeda S, Matsuo M, Osuga Y. The EZH2-PRC2-H3K27me3 axis governs the endometrial cell cycle and differentiation for blastocyst invasion. *Death Dis*. 2023 May 18;14(5):320.
 10. Chiba Y, Nose-Ogura S, Sekiguchi K, Eda K, Nakamura H, Koshimizu T, Yamamoto H, Yamaguchi T, Harada M, Wada-Hiraike O, Osuga Y. Development of University of Tokyo's eating disorders inventory in female athletes. *J Obstet Gynaecol Res*. 2023 Jul;49(7):1854-1866.
 11. Urata Y, Salehi R, Wyse BA, Jahangiri S, Librach CL, Tzeng CR, Osuga Y, Tsang B. Neuropeptide Y directly reduced apoptosis of granulosa cells, and the expression of NPY and its receptors in PCOS subjects. *J Ovarian Res*. 2023 Aug 31;16(1):182.
 12. Hisano M, Nakagawa K, Ono M, Yoshino O, Saito T, Hirota Y, Inoue E, Kikuchi K, Nakamura H, Yamaguchi K. Multicenter, 2-dose single-group controlled trial of tacrolimus for the severe infertility patients. *Medicine (Baltimore)*. 2023 Aug 11;102(32):e34317.
 13. Hiratsuka D, Omura E, Ishizawa C, Iida R, Fukui Y, Hiraoka T, Akaeda S, Matsuo M, Harada M, Wada-Hiraike O, Osuga Y, Hirota Y. Pregnancy is associated with reduced progression of symptomatic adenomyosis: a retrospective pilot study. *BMC Pregnancy Childbirth*. 2023 Sep 4;23(1):634.
 14. Ono M, Harada M, Horie A, Dai Y, Horiguchi I, Kikuchi E, Kimura F, Koizumi T, Komeya M, Mizunuma N, Oseto K, Ota K, Shimizu C, Sugimoto K, Takae S, Takeuchi E, Nishi H, Yumura Y, Furui T, Takai Y, Morishige KI, Watanabe C, Osuga Y, Suzuki N. Effect of a web-based fertility preservation training program for medical professionals in Japan. *Int J Clin Oncol*. 2023 Sep;28(9):1112-1120.
 15. Hiraoka T, Osuga Y, Hirota Y. Current perspectives on endometrial receptivity: A comprehensive overview of etiology and treatment. *J Obstet Gynaecol Res*. 2023 Oct;49(10):2397-2409.
 16. Harada S, Yamada M, Shirasawa H, Jwa SC, Kuroda K, Harada M, Osuga Y. Fact-finding survey on assisted reproductive technology in Japan. *J Obstet Gynaecol Res*. 2023 Nov;49(11):2593-2601.
 17. Takeshige Y, Jwa SC, Hirota Y, Osuga Y, Kuramoto T, Mio Y, Furui K, Kinutani M, Shiotani M, Asada Y, Kamiya H, Yoshida H, Igarashi H, Kyono K. Clinical outcomes of personalized blastocyst embryo transfer after

-
- endometrial receptivity analysis: A multicenter, retrospective cohort study. *Reprod Med Biol.* 2023 Nov 29;22(1):e12550.
18. Katagiri Y, Jwa SC, Kuwahara A, Iwasa T, On M, Kato K, Kishi H, Kuwabara Y, Taniguchi F, Harada M, Iwase A, Osuga Y. Assisted reproductive technology in Japan: A summary report for 2021 by the Ethics Committee of the Japan Society of Obstetrics and Gynecology. *Reprod Med Biol.* 2023 Dec 30;23(1):e12552.
19. Xu Z, Takahashi N, Harada M, Kunitomi C, Kusamoto A, Koike H, Tanaka T, Sakaguchi N, Urata Y, Wada-Hiraike O, Hirota Y, Osuga Y. The Role of Cellular Senescence in Cyclophosphamide-Induced Primary Ovarian Insufficiency. *Int J Mol Sci.* 2023 Dec 6; 24(24):17193.

Reproductive, Developmental and Aging Sciences

2. Pediatric Sciences

Department of Pediatrics, Department of Developmental Pediatrics

Professor

Motohiro Kato, M.D., Ph.D.

Naoto Takahashi, M.D., Ph.D. (Department of Pediatric and Neonatal Intensive Care Unit)

Associate Professor

Yutaka Harita, M.D., Ph.D., Hikoro Matsui M.D., Ph.D.

Lecturer

Ryo Inuzuka, M.D., Ph.D., Shoichiro Kanda, M.D., Ph.D., Kohei Kashima, M.D., Ph.D.
(Department of Maternal, Fetal and Neonatal Medicine)

Project Lecturer

Atsushi Sato, M.D., Ph.D., Yuko Kajiho, M.D., Ph.D., Akiko Kinumaki, M.D., Ph.D.

Research Associate

Mami Kobayashi, M.D., Takako Matsuoka, M.D., Ph.D., Shunpei Uchino, M.D., Ph.D.,
Hiroshi Terashima, M.D., Takanobu Inoue, M.D., Ph.D., Hitomi Masuda, M.D.,
Yoshihiko Shitara, M.D., Takeo Mukai, M.D., Ph.D., Atsushi Ito, M.D., Ph.D.,
Kentaro Watanabe, M.D., Ph.D., Yu Tanaka, M.D., Ph.D., Takuya Oshima, M.D.,
Hiroshi Muto, M.D., Mieko Maezawa, M.D., Kazuhiro Shiraga, M.D.,
Kenichiro Hayashi, M.D., Masahiro Sekiguchi, M.D., Ph.D., Hiroyuki Tanaka, M.D., Ph.D.,
Yu Kakimoto, M.D., Hidetoshi Ohta, M.D., Moe Hidaka, M.D., Kaname Uchida, M.D.,
Koji Hirohata, M.D., Yosuke Ogawa, M.D., Hisataka Nozawa, M.D., Yuriko Katayama,
M.D., Koichi Takamizawa, M.D., Kaname Sato, M.D., Kyosuke Ibi, M.D., Natsuho Adachi,
M.D., Hiroki Kitaoka M.D., Ayumi Kunikata, M.D., Shutaro Inoue, M.D., Yui Ozawa, M.D.,
Marina Tanaka, M.D., Kumiko Uryu, M.D., Rumi Taniguchi, M.D., Yukiko Kuroda, M.D.,
Akiko Shibata, M.D., Miyuki Ota M.D., Etsushi Toyofuku, M.D., Satoko Kobayashi, M.D.,
Ayami Sato, M.D., Keiko Watanabe, M.D.
(As of March 31, 2023)

※The following information is the same as that of the previous year for certain reasons.

Homepage <http://square.umin.ac.jp/ped/>

Introduction and Organization

The Department of Pediatrics and the Department of Developmental Pediatrics are sub-divisions of the Reproductive, Developmental and Aging Medicines, at the Graduate School of Medicine at The University of Tokyo. Our staff consists of 2 professors, 2 associate professors, 3 lecturers, 3 project lecturers, 34 research associates on March 31, 2023.

Our outpatient services are housed on the second floor of the outpatient clinic building, while inpatient care is offered at the Pediatric Medical Center located in the inpatient building. Our administrative offices are located at the second floor of the East Research Building. Additionally, our laboratories are situated on the seventh floor of the Clinical Research Center and on the second and third floors of the East Research Building.

Our departments are dedicated to providing high-quality clinical care, teaching, and research in pediatrics and developmental pediatrics. We continually strive to improve our services and offerings to meet the evolving needs of our patients, their families, and the broader community. Our ultimate aim is to become a leading center for pediatric and developmental medical care, not only in Tokyo but also on a global scale.

Clinical activities

Our outpatient pediatric clinics provide care across a broad spectrum of pediatric disorders, including but not limited to hematology/oncology, cardiology, neurology, nephrology, endocrinology, and neonatology. Moreover, patients with conditions related to genetics, pulmonology, and allergology/immunology are attended to by part-time physicians specializing in each field. Additionally, we maintain continuity of care post-discharge through our outpatient clinics, coordinating care that aligns with the specific needs of patients and their families through partnerships with local medical institutions.

We operate specialized clinics covering all fields of pediatric disorders. Pediatric and neonatal patients are admitted to the Pediatric Medical Center where they receive targeted treatments. Since June 2019, we have intensified our focus on critical care, culminating in the establishment of the section for Pediatric and

Perinatal Intensive Care. This includes a Neonatal Intensive Care Unit (NICU) with 21 beds and a Pediatric Intensive Care Unit (PICU) with 12 beds, serving as one of the tertiary centers for pediatric emergencies in the eastern part of Tokyo. Our PICU delivers state-of-the-art monitoring and comprehensive care for children suffering from critical illnesses or injuries, and those with complex medical conditions.

In our NICU and Growing Care Unit (GCU), which has 36 beds, we care for high-risk infants, including premature babies weighing under 500 grams and newborns requiring invasive interventions for congenital disorders. We offer high-quality, specialized medical care as a leading perinatal center in Tokyo, involving multi-disciplinary collaboration with obstetricians, pediatric cardiologists, cardiac surgeons, pediatric surgeons, ophthalmologists, neurosurgeons, among others. Our approach also incorporates family-centered care through coordination with co-medical staff.

In the general ward of the Pediatric Medical Center, we provide comprehensive care for children suffering from a wide range of conditions including hematological/oncological disorders, cardiac conditions, neuromuscular issues, immunological diseases, renal and urinary tract diseases, endocrinological conditions, metabolic disorders, and psychosomatic diseases. This is done in collaboration with related departments. Additionally, our hospital has received accreditation as a provider of chimeric antigen receptor T-cell therapy.

We offer a comprehensive package of support services. These include subsidized housing through McDonald House, an on-site school to help young patients continue their education, and a variety of additional services such as psychosocial support for families, translation services, and volunteer groups.

Teaching activities

M2 students are given pediatric systematic lectures covering each specialty area. M3 students undergo a 2-week participatory ward training (M3 Clinical Clerkship). During the training period, students are assigned to each clinical team and are in charge of

inpatients, taking their medical history, examining them, recording their admission records, and observing various specialized examinations. During the internship in the pediatric ward, the students will do cruises in pediatric neurology, nephrology, transfusion, endocrinology, neonatology, hematology/oncology, cardiology, emergency resuscitation, and others. On Tuesdays, the students will be exposed to and discuss pediatric cases as a whole through online rounds of chart rounds. During the second week of the internship, each student will present their assigned cases to foster experience in presentation skills and question and answer sessions. The M4 clinical clerkship is a one-month program that provides highly specialized training that cannot be experienced in the two-week ward training. Pediatrics with a focus on the typical development of healthy children. The professor or associate professor conducts an examination on the last day. In addition, students are provided with online learning content through the pediatrics educational website.

Research activities

Our research divisions focus on nephrology, hematology/oncology, neurology, cardiology, endocrinology/metabolism, immunology/allergy, and neonatology. We also operate interdisciplinary research groups that focus on areas like cell biology, genetic molecular biology, and epidemiology. The highlights of our research activities over the past year are as follows:

Hematology/Oncology group:

Our division has performed whole-genome sequencing (WGS), whole-exome sequencing (WES), and RNA-sequencing to characterize the genetic landscapes of several pediatric cancers, including leukemia, brain tumors, and soft tissue sarcomas.

Nephrology group:

Our aim is to reveal the molecular mechanism of pediatric kidney diseases. We identified novel causative mutations on several proteinuric diseases including pediatric nephrotic syndrome and congenital anomalies of the kidney and urinary tract. We are also developing a novel urinary test using urinary extracellular vesicles.

Endocrinology and Metabolism group:

We are analyzing genes and mechanisms involved in endocrinology and metabolic diseases. We analyze the molecular biological mechanisms using model animals and iPS cells. We are also studying pathways in growth plate cartilage in relation to pediatric growth and development, including single-cell RNA analysis using mouse and human specimens.

Cardiology group:

To reveal the molecular mechanism of cardiomyopathy, we performed genome-wide association studies and generated an animal model for cardiomyopathy. Additionally, we perform hemodynamic analysis for patients with congenital heart disease using clinical imaging modalities.

Neurology Group:

After a clinical trial of valganciclovir for congenital cytomegalovirus infection has shown therapeutic efficacy for recovering hearing difficulty, we continue to follow up on hearing and psychomotor development.

Neonatology group:

Epigenetic changes in cord blood and postnatal peripheral blood of preterm and SGA infants are investigated using epigenome-wide methylation analysis. The influence of gut microbiome on neonatal immune function and nutritional status is also investigated. Cytokine profiles have been investigated in order to elucidate pathophysiology of several diseases in perinatal period. Molecular mechanism of neonatal immune tolerance is also an important research topic in the group.

PICU group:

The Pediatric Intensive Care Unit (PICU) Group promotes research originating from clinical practice. The group conducts research directly related to understanding, evaluating, and treating pathological conditions in clinical practice, including biological response research using bedside physiological data, such as heart rate variability analysis, quantification of nerve reflexes, evaluation of cerebral blood flow regulation, and pulse wave analysis; medical safety research using DWH; development of new diagnostic equipment and evaluation systems using AI; and development of novel bedside digital fundoscope. We are conducting research directly related to the understanding, evaluation, and treatment of pathological conditions in clinical practice.

Selected References

1. Takizawa K, Ueda K, Sekiguchi M, Nakano E, Nishimura T, Kajiho Y, Kanda S, Miura K, Hattori M, Hashimoto J, Hamasaki Y, Hisano M, Omori T, Okamoto T, Kitayama H, Fujita N, Kuramochi H, Ichiki T, Oka A, Harita Y. Urinary extracellular vesicles signature for diagnosis of kidney disease. *iScience*. 25(11): 105416, 2022
2. Nakamura M, Kanda S, Kajiho Y, Hinata M, Tomonaga K, Fujishiro J, Harita Y. A case of right hypodysplastic kidney and ectopic ureter associated with bicornuate uterus in a prepubertal girl. *CEN Case Rep*. 12(1):122-129, 2023
3. Miura K, Kaneko N, Hashimoto T, Ishizuka K, Shirai Y, Hisano M, Chikamoto H, Akioka Y, Kanda S, Harita Y, Yamamoto T, Hattori M. Precise clinicopathologic findings for application of genetic testing in pediatric kidney transplant recipients with focal segmental glomerulosclerosis/steroid-resistant nephrotic syndrome. *Pediatr Nephrol*. 38(2):417-429, 2023
4. Critical brainstem encephalitis/encephalopathy in a child with COVID-19. Kunikata A, Hayashi K, Kinumaki A, Akatsuka Y, Shimoda K, Kato M, Matsui H. *Pediatr Int*. 64 : e15353, 2022
5. Circulating nephrin autoantibodies and posttransplant recurrence of primary focal segmental glomerulosclerosis. Hattori M, Shirai Y, Kanda S, Ishizuka K, Kaneko N, Ando T, Eguchi M, Miura K. *Am J Transplant*. 2022 Oct; 22(10):2478-2480. doi: 10.1111/ajt.17077.
6. Urinary extracellular vesicles signature for diagnosis of kidney disease. Takizawa K, Ueda K, Sekiguchi M, Nakano E, Nishimura T, Kajiho Y, Kanda S, Miura K, Hattori M, Hashimoto J, Hamasaki Y, Hisano M, Omori T, Okamoto T, Kitayama H, Fujita N, Kuramochi H, Ichiki T, Oka A, Harita Y. *iScience*. 2022 Nov 8;25(11): 105416. doi: 10.1016/j.isci.2022.105416.
7. Ibi K, Takahashi N. Assisted reproductive technology and neonatal intensive care unit: A retrospective observational study from a single center. *J Obstet Gynaecol Res*. 2023 Jan;49(1): 273-279. doi: 10.1111/jog.15478. Epub 2022 Oct 25.
8. Takahashi N, Shoji H, Arai H, Tanaka K, Kakiuchi S, Yoda H, Shimizu T. Effect of biotin supplementation in infant formula: A multi-center study in Japan. *Pediatr Int*. 2023 Jan; 65(1):e15359. doi: 10.1111/ped.15359.
9. Morioka I, Kakei Y, Omori T, Nozu K, Fujioka K, Takahashi N, Yoshikawa T, Moriuchi H, Ito Y, Oka A; Japanese Congenital
10. Cytomegalovirus Study Group. Oral Valganciclovir Therapy in Infants Aged ≤ 2 Months with Congenital Cytomegalovirus Disease: A Multicenter, Single-Arm, Open-Label Clinical Trial in Japan. *J Clin Med*. 2022 Jun 21; 11(13):3582. doi: 10.3390/jcm11133582.
11. Inuzuka R, Nii M, Inai K, Shimada E, Shinohara T, Kogiso T, Ono H, Otsuki SI,
12. Kurita Y, Takeda A, Hirono K, Takei K, Yasukohchi S, Yoshikawa T, Furutani Y, Shinozaki T, Matsuyama Y, Senzaki H, Tokushige K, Nakanishi T. Predictors of liver cirrhosis and hepatocellular carcinoma among perioperative survivors of the Fontan operation. *Heart*. 2023 Jan 27;109(4):276-282.
13. Dimopoulos K, Constantine A, Clift P, Condliffe R, Moledina S, Jansen K, Inuzuka R, Veldtman GR, Cua CL, Tay ELW, Opatowsky AR, Giannakoulas G, Alonso-Gonzalez R, Cordina R, Capone G, Namuyonga J, Scott CH, D'Alto M, Gamero FJ, Chicoine B, Gu H, Limsuwan A, Majekodunmi T, Budts W, Coghlan G, Broberg CS; for Down Syndrome International (DSi). Cardiovascular Complications of Down Syndrome: Scoping Review and Expert Consensus. *Circulation*. 2023 Jan 31;147(5):425-441.
14. Omori A, Inuzuka R, Matsui H, Hirata Y. Aortic and bronchial perforation caused by a vascular clip 3 years after its placement. *Eur J Cardiothorac Surg*. 2022 Sep 2;62(4):ezac457.
15. Watanabe K, Kimura S, Seki M, Isobe T, Kubota Y, Sekiguchi M et al. Identification of the ultrahigh-risk subgroup in neuroblastoma cases through DNA methylation analysis and its treatment exploiting cancer metabolism. *Oncogene*. 2022;41:4994-5007.
16. Isobe T, Takagi M, Sato-Otsubo A, Nishimura A, Nagae G, Yamagishi C et al. Multi-omics

analysis defines highly refractory RAS burdened immature subgroup of infant acute lymphoblastic leukemia. *Nature communications*. 2022;13:4501.

17. Hiwatari M, Seki M, Matsuno R, Yoshida K, Nagasawa T, Sato-Otsubo A et al. Novel TENM3-ALK fusion is an alternate mechanism for ALK activation in neuroblastoma. *Oncogene*. 2022;41:2789-97.

Department of Pediatric Surgery

Professor

Jun Fujishiro, M.D., Ph.D.

Lecturer

Mariko Yoshida, M.D., Ph.D. Shinya Takazawa, M.D., Ph.D.

Research Associate

Kenichiro Konishi, M.D., Ph.D. Toshiko Takezoe, M.D., Ph.D. Keisuke Suzuki, M.D., Ph.D. Tomohiro Sunouchi, M.D. Akinori Ichinose, M.D. Takashi Tsutsuno, M.D.

※The following information is the same as that of the previous year for certain reasons.

Homepage pedsurg.umin.jp/

History and organization

In 1951, a pediatric surgical team was established in the Department of Second Surgery. Subsequently, in 1961, a pediatric surgical research team, which would eventually research diaphragmatic hernia, was established, with a chief, Dr. Ishida, appointed by Professor Kimoto.

In 1971, the department was authorized to be the first clinical Department of Pediatric Surgery at a national university.

A pediatric intensive care unit was founded by Prof. Ishida in 1973, and the construction of a ward capable of accommodating mainly pediatric surgical patients was completed.

Assistant Prof. Saito assumed office as the first director of this clinical department.

Dr. Sumio Saito became a professor of pediatric surgery in 1983. Professor Saito has enthusiastically performed clinical studies on operation techniques and the use of biliary atresia.

Dr. Toshio Nakajo took office as a professor in 1985. Prof. Nakajo has developed original operative procedures, such as a radical operation for umbilical hernia, and an anti-reflex valve for biliary atresia. These original operative procedures have since been inherited by other pediatric surgeons as Nakajo

methods.

Our department was authorized as the Department of Pediatric Surgery of Kyusyu University by the Ministry of Education in 1989.

Dr. Yoshiaki Tsuchida assumed the role of Professor in 1990 and published many highly regarded articles, mainly concerning neuroblastoma and Wilm's tumor, based on his research and clinical work.

In 1995, the department was reorganized as the Department of Reproductive, Developmental and Aging Science, Pediatric Science and Pediatric Surgery, due to a university policy for the graduate school.

In 1997, Dr. Kohei Hashizume became a professor in the Department of Pediatric Surgery. He started performing living-related partial liver transplantation (LRPLT) for children with Professor Makuuchi in the Department of Second Surgery.

Dr. Tadashi Iwanaka became the sixth professor in August 2006. He engaged in clinical and research activity on pediatric minimally invasive surgery, and retired in 2015. In 2016, Associate Prof. Jun Fujishiro became a chief of the department of pediatric surgery of Tokyo University. In 2019, Dr. Fujishiro promoted to a professor from an associate professor.

The present staff includes one professor and chief, two lecturers, four research associates and nine graduate

students. More than 20 members of our department shoulder the clinical work as pediatric surgeons.

Clinical activities

Staff members higher than the level of research associate take charge of the outpatient clinic from Monday through Friday. The pediatric surgical outpatient clinic takes place in the same location as the pediatric outpatient clinic, and we closely cooperate with pediatricians to diagnose and treat patients. We also have specialized outpatient clinics, liver and biliary tract clinics, a tumor clinic, and a spina bifida clinic. Recently, a second-opinion clinic opened to provide careful detailed explanations, and this has received a favorable reception.

Our ward was transferred to the hospital's second floor of B wing from the second floor of south of the A wing on January 2018. Other pediatric surgical patients also are admitted to this ward. We have seven beds in the ward, and about 300 patients a year are hospitalized within it. Most operation cases are inguinal hernia, but we manage other cases such as respiratory surgery disease, neonatal digestive organ obstructions, infant malignant tumors such as Wilms' tumor and neuroblastoma, biliary tract diseases such as biliary tract dilatation and biliary atresia, respiratory anomalies such as tracheal stenosis and lung cysts, gastrointestinal anomalies, and urological disorders including hydronephrosis and vesicoureteral reflux.

We work with other pediatric surgery teams at other institutions who perform endoscopic surgery (laparoscopic surgery/thoracoscopic surgery). We have developed an endoscopic surgery technique for pediatric diseases not covered by insurance, for cases requiring advanced medical care. Furthermore, we surgically manage seriously ill, mentally and physically handicapped infants, as well as patients with intractable nervous system diseases, to improve their quality of life, and we cooperate with pediatricians (neonatologists) to treat patients with prenatal diagnoses.

Education

We expose first and second year students to our daily clinical work, as well as to our research work, during

the "Free Quarter" and "Research Lab Visit" courses. These students are guided to be concerned with clinical areas, and are in charge of parts of various research projects. The students hold a results announcement party at the end of training. For M2 students, general pediatric surgery and neonatal surgery instruction is provided by the associate professor and the lecturer.

An education program is also provided for M3 and M4 students for five days.

The bedside education of pediatric surgery consists of participation in clinical conferences, attendance at operations, and small group lectures concerning neonatal surgery; pediatric surgical oncology; pediatric hepatobiliary surgery; and pediatric emergency medicine, which includes the practice of performing cardiac massage and intra-tracheal intubation using mannequins for practice.

Additionally, we take charge of the core surgical curriculum during the "super-rotation" postgraduate training. We offer a program in which each resident can learn basic knowledge about pediatric surgical disease and surgery and hemodynamic and respiratory evaluation, as well as basic surgical techniques and patient management strategies.

Research activities

There are two pillars of the research projects in our group recently. One is the elucidation of the course and the development of new therapy of pediatric surgical disease using proteome analysis. The other is the clinical research using NCD (National Clinical Database). The results of these studies has been already announced in some articles.

We concentrate power on the study for the pathophysiology of biliary atresia and approach it from many aspects including an animal model, disease-specific iPS cells, and the search of the biomarkers.

In addition, We now goes a research of the organ regeneration using in-body tissue architecture and start diaphragm and the trachea and gastrointestinal reproduction from bio-sheet or bio-tube technology.

References

- 1) Yamaguchi K, Horie C, Takane K, Ikenoue T,

- Nakagawa S, Isobe Y, Ota Y, Ushiku T, Tanaka M, Fujishiro J, Hoshino N, Arisue A, Nishizuka S, Aikou S, Shida D, Furukawa Y.
Identification of odontogenic ameloblast associated as a novel target gene of the Wnt/ β -catenin signaling pathway.
Cancer Sci. 2022; 00: 1- 13. doi:10.1111/cas.15657
- 2) Sukezaki A, Kato S, Makise N, Watadani T, Fujishiro J.
Pseudotumoral cystitis mimicking malignancy in a child.
Pediatr Int. 2022; 64(1):e15160. doi:10.1111/ped.15160. PMID: 35616154
 - 3) Sakaguchi H, Konishi K, Yasuda R, Sasaki H, Yoshimaru K, Tainaka T, Fukahori S, Sanada Y, Iwama I, Shoji H, Kinoshita M, Matsuura T, Fujishiro J, Uchida H, Nio M, Yamashita Y, Mizuochi T.
Serum matrix metalloproteinase-7 in biliary atresia: a Japanese multicenter study
Hepatol Res. 2022; ;52(5):479-487. doi: 10.1111/hepr.13753. PMID: 35106887
 - 4) Kawano T, Souzaki R, Sumida W, Ishimaru T, Fujishiro J, Hishiki T, Kinoshita Y, Kawashima H, Uchida H, Tajiri T, Yoneda A, Oue T, Kuroda T, Koshinaga T, Hiyama E, Nio M, Inomata Y, Taguchi T, Ieiri S.
Laparoscopic approach for abdominal neuroblastoma in Japan: results from nationwide multicenter survey.
Surg Endosc. 2022; 36(5): 3028-3038. doi: 10.1007/s00464-021-08599-4. PMID: 34143289
 - 5) Yamamoto S, Ikeda M, Ohama Y, Sunouchi T, Hoshino Y, Ito H, Yamashita M, Kanno Y, Okamoto K, Yamagoe S, Miyazaki Y, Okugawa S, Fujishiro J, Moriya K.
Aureobasidium melanigenum catheter-related bloodstream infection: a case report.
BMC Infect Dis. 2022; 22(1):335. doi: 10.1186/s12879-022-07310-9. PMID: 35382751
 - 6) Omata K, Yoshida M, Suzuki K, Kawashima H, Fujishiro J.
Ectopic gallbladder with congenital biliary dilatation: a pediatric case report.
Surg Case Rep. 2022; 8(1):51. doi: 10.1186/s40792-022-01401-0. PMID: 35347468
 - 7) Li Y, Watanabe E, Kawashima Y, Plichta DR, Wang Z, Ujike M, Ang QY, Wu R, Furuichi M, Takeshita K, Yoshida K, Nishiyama K, Kearney SM, Suda W, Hattori M, Sasajima S, Matsunaga T, Zhang X, Watanabe K, Fujishiro J, Norman JM, Olle B, Matsuyama S, Namkoong H, Uwamino Y, Ishii M, Fukunaga K, Hasegawa N, Ohara O, Xavier RJ, Atarashi K, Honda K.
Identification of trypsin-degrading commensals in the large intestine.
Nature. 2022 Sep; 609(7927): 582-589. doi: 10.1038/s41586-022-05181-3. Epub 2022 Sep 7. PMID: 36071157
 - 8) Watanabe E, Ota H, Takasugi N, Hiwatari M, Fujishiro J
A school-aged case of intratumor bleeding of an adrenal neuroblastoma rescued by transcatheter atrial embolization.
Pediatr Int. 2022 Jan;64(1):e14987. doi: 10.1111/ped.14987. PMID: 35312221
 - 9) Fujiogi M, Konishi T, Michihata N, Hashimoto Y, Matsui H, Ishimaru T, Fushimi K, Yasunaga H, Fujishiro J.
Perioperative outcomes of thyroid cancer surgery in children and adults: a nationwide inpatient database study in Japan.
Ann Clin Epidemiol 2022, <https://doi.org/10.37737/ace.23004>
 - 10) Misako Nakamura , Shoichiro Kanda , Yuko Kajiho , Munetoshi Hinata , Kotaro Tomonaga , Jun Fujishiro , Yutaka Harita
A case of right hypodysplastic kidney and ectopic ureter associated with bicornuate uterus in a prepubertal girl
CEN Case Rep., 2023 Feb;12(1):122-129. doi: 10.1007/s13730-022-00730-1.
 - 11) Ishimaru T, Fujiogi M, Michihata N, Konishi T, Morita K, Matsui H, Uda K, Fushimi K, Kawashima H, Fujishiro J, Yasunaga H
Perioperative outcomes of laparoscopically assisted anorectoplasty versus conventional procedures for anorectal malformation: a retrospective nationwide database study.
Pediatr Surg Int. 2022;38(12):1785-1791. doi: 10.1007/s00383-022-05234-8. PMID: 36102983
 - 12) Asai A, Wu JF, Wang KS, Yamataka A, Nio M, Su DJ, Short C, Tsuboi K, Ochi T, Sasaki H,

- Okubo R, Yodoshi T, Konishi K, Rogers ME, Tiao GM
The Outcome of Patients With Cystic Biliary Atresia With Intact Proximal Hepatic Ducts Following Hepatic-Cyst-Jejunostomy.
J Pediatr Gastroenterol Nutr. 2022 Aug 1;75(2): 131-137.
- 13) Konishi KI, Suzuki K, Komura M, Kudo H, Ishimaru T, Sugiyama M, Komuro H, Iwanaka T, Fujishiro J.
Endoscopic nasobiliary drainage tube insertion for treatment of afferent loop obstruction in a pregnant woman after Kasai portoenterostomy.
J Pediatr Surg Case Rep. Volume 78, March 2022, 102194.
- 14) Sakaguchi H, Konishi KI, Yasuda R, Sasaki H, Yoshimaru K, Tainaka T, Fukahori S, Sanada Y, Iwama I, Shoji H, Kinoshita M, Matsuura T, Fujishiro J, Uchida H, Nio M, Yamashita Y, Mizuochi T.
Serum matrix metalloproteinase-7 in biliary atresia: A Japanese multicenter study.
Hepatol Res. 2022 Feb 1.
- 15) Morita K, Fujiogi M, Michihata N, Matsui H, Fushimi K, Yasunaga H, Fujishiro J.
Oral Antibiotics and Organ Space Infection after Appendectomy and Intravenous Antibiotics Therapy for Complicated Appendicitis in Children.
Eur J Pediatr Surg. 2022 Dec 28. doi: 10.1055/a-1958-7915. PMID: 36220134
- 16) Marques Marinho M, Oikawa R, Hayashi K, Takazawa S, Harada K, Mitsuishi M.
Design and validation of looping assistance methods in robotic-assisted neonatal surgical suturing in a chest model
Int J Med Robot. 2022 Oct 27;e2476. doi: 10.1002/rcs.2476.
- 17) Hayashi K, Mori M, Sanmoto Y, Oiki H, Ishimaru T, Arakawa Y, Koh K, Kawashima H.
Relationship between the timing of chemotherapy and surgical complications following surgical biopsy in children with malignant solid tumors
Pediatr Blood Cancer. 2023 Jan;70(1):e30030. doi: 10.1002/pbc.30030.
- 18) Naohiro Takamoto, Shinya Takazawa, Yuki Yoshida, Tamotus Sasaki, Akira Nishi
Examination of the effectiveness of bedside nasojejunal tube placement using a portable imaging device with a flat panel detector
Nagoya J Med. Sci. 84. 772-781, 2022

Reproductive, Developmental and Aging Sciences

3. Aging Sciences

Department of Geriatric Medicine

Department of Aging Research

Professor

Masahiro Akishita, MD, PhD.

Associate Professor

Sumito Ogawa, MD, PhD.

Lecturer

Taro Kojima, MD, PhD.

Masaki Ishii, MD, PhD.

Kotaro Azuma, MD, PhD.

Research Associate

Mitsutaka Yakabe, MD, PhD.

Michiko Nanao, MD, PhD.

Yoko Yamada, MD, PhD.

Tatsuya Hosoi, MD, PhD.

※The following information is the same as that of the previous year for certain reasons.

Homepage <https://www.h.u-tokyo.ac.jp/english/centers-services/clinical-divisions/geriatric-medicine/index.html> (English)
<http://geriatrics.umin.jp/> (Japanese)

Introduction and Organization

The Department of Geriatric Medicine was established in 1962, as the first geriatric department in Japan.

Since older adult patients tend to have multiple organ disorders, these patients should be taken cared as a whole from multiple points of view. In addition, symptoms, signs and responses to the treatment in the older adult patients could be quite different from the younger counterparts. Specific knowledge on the physiological and metabolic changes with aging is necessary when these older adult patients are treated. Quality of life of the patients is another point of view which should be emphasized. The department belongs to the division of Internal Medicine. The staff includes one professor, one associate professor, three lecturers, and four assistant professors.

Our sub-specialty includes pneumology, cardiology,

neurology, hematology, endocrinology, and bone metabolism, besides geriatrics. The main objective of our research is to elucidate the pathophysiology of aging process and to understand older adult patients from viewpoints of basic aging science using molecular biology technique and clinical aspects using the recent advancement of technology and geriatric assessment.

Clinical activities

The Department of Geriatric Medicine specialized in the diagnosis and treatment of dementia, frailty, geriatric syndrome and polypharmacy in older adults. We provide Comprehensive Geriatric Assessment (CGA) and manages multiple diseases in older patients who have physical and/or mental disabilities. The Department of Geriatric Medicine belongs to Internal Medicine. In the outpatient setting, we accept

patients every day in the three outpatient wards (#207, #208, and #209). We also provide specialized outpatient treatment on dementia, frailty and sarcopenia, osteoporosis, chronic obstructive pulmonary disease (COPD), and sleep apnea. As a 'second opinion outpatient clinic', we accept consultation on polypharmacy. Since 2003, we provide 'women's general outpatient clinic' by female physicians for treatment of gender sensitive conditions. In the inpatient setting, we have our proper wards in the 13th floor of our hospital, and generally accept approximately 10 patients who are treated by junior, senior, and chief residents of our staff. Older patients often suffer from a variety of diseases and clinical problems. To deal with them, our department forms multi-disciplinary teams composed of geriatricians and related specialists such as psychologists and pharmacists to provide comprehensive medical care.

Education

Clinical education is provided for fifth- and sixth-year medical students on a man-to-man basis with a faculty staff member. During the period, the student studies one or two cases, through which the student learns the techniques of interrogation and physical examination, interpretation of laboratory tests, and actual medical procedures. Interpretation of the results of geriatric assessment is studied through lectures in a case-oriented manner with an emphasis placed on the multidisciplinary basis of geriatric patients.

Research

The purpose of our study is to fulfill the society where older adult people enjoy healthy independent life. We are engaged in studies on various topics including epidemiological studies, clinical studies, and basic molecular studies to contribute to our research aim. Our main research themes are as follows.

- 1) Research on the molecular mechanism of vascular calcification
- 2) Regulation of vascular function by sex hormone
- 3) Molecular biology for the control of aging: Association of vascular and neuronal senescence and the role of Sirt1
- 4) Molecular biology and treatment of sarcopenia
- 5) Multicenter-investigation of the optimal treatment strategy for hypertension or lipid disorder in the older adult patients
- 6) Clinical study on metabolic syndrome in the older adult patients
- 7) Research on the appearance of patients with cognitive impairment; Development of AI model which detects cognitive impairment from the facial expression
- 8) Research on appropriate healthcare for the older adult patients including pharmacotherapy
- 9) Expression and regulation of nuclear receptors in osteoblast and osteoclast
- 10) Molecular mechanism under the treatment of osteoporosis
- 11) Genetic analysis of osteoporosis and osteoarthritis
- 12) Identification and functional analysis of the target gene networks associated with hormone responsiveness in prostate and breast cancers
- 13) Roles of nuclear receptors in age-related diseases and cancers
- 14) Molecular mechanism of vitamin K function and its roles in aging
- 15) Novel roles of antimicrobial peptide, defensin
- 16) Adrenomedullin and airway hyperresponsiveness
- 17) Klotho protein and vitamin D in lung
- 18) Clinical investigation of sleep-related breathing disorder
- 19) Observational study on medical treatment/care provided in the end-of-life stage of life
- 20) Observational study on the outcome of frail patients
- 21) Clinical study on the relationship between
- 22) metabolic diseases and pulmonary aging

Publications (Original Articles)

1. Akashi S, Oguri M, Ikeno E, Manita M, Taura J, Watanabe S, Hayashi T, Akao M, Okumura K, Akishita M, Yamashita T. Outcomes and Safety of Very-Low-Dose Edoxaban in Frail Patients With Atrial Fibrillation in the ELDERCARE-AF Randomized Clinical Trial. *JAMA Netw Open*. 2022;5:e2228500.
2. Akishita M, Suzuki S, Inoue H, Akao M,

- Atarashi H, Ikeda T, Koretsune Y, Okumura K, Shimizu W, Tsutsui H, Toyoda K, Hirayama A, Yasaka M, Yamaguchi T, Teramukai S, Kimura T, Morishima Y, Takita A, Yamashita T. Frailty and outcomes in older adults with non-valvular atrial fibrillation from the ANAFIE registry. *Arch Gerontol Geriatr*. 2022;101:104661.
3. Azuma K, Osuka Y, Kojima N, Sasai H, Kim H, Inoue S. Association of Vitamin K Insufficiency as Evaluated by Serum Undercarboxylated Osteocalcin With Frailty in Community-Dwelling Older Adults. *Front Aging*. 2022;3:865178. doi: 10.3389/fragi.2022.865178.
 4. Chen LK, Iijima K, Shimada H, Arai H. Community re-designs for healthy longevity: Japan and Taiwan examples. *Arch Gerontol Geriatr*. 2022 23;104875, doi: 10.1016/j.archger.2022.104875.
 5. Fujikawa H, Son D, Aoki T, Kondo K, Takemura Y, Saito M, Den N, Eto M. Translating and validating a Japanese version of the instrument for patient assessment of medical professionalism (J-IPAMP): a cross-sectional survey. *BMC Med Edu*. 2022;22:641. doi: 10.1186/s12909-022-03699-8.
 6. Fujikawa H, Son D, Aoki T, Eto M. Association between patient care ownership and personal or environmental factors among medical trainees: a multicenter cross-sectional study. *BMC Med Edu*. 2022;22:666. doi: 10.1186/s12909-022-03730-y.
 7. Fujikawa H, Eto M. What Is the Optimal Amount of Supervision to Induce Residents to Develop Patient Care Ownership? *Acad Med*. 2022;97:1578. doi: 10.1097/ACM.0000000000004927.
 8. Fujikawa H, Mitsuyama T, Son D, Izumiya M, Eto M. Development and Validation of a Performance Assessment Checklist Scale for Vaccine Administration. *Int Med*. 2022. doi: 10.2169/internalmedicine.9268-21.
 9. Hattori Y, Hamada S, Yamanaka T, Kidana K, Iwagami M, Sakata N, Tamiya N, Kojima T, Ogawa S, Akishita M. Drug prescribing changes in the last year of life among homebound older adults: national retrospective cohort study. *BMJ Support Palliat Care*. 2022. Jul 13: bmjspcare-2022-003639. doi: 10.1136/spcare-2022-003639. Epub ahead of print. PMID: 35831182.
 10. Hattori Y, Hamada S, Ishizaki T, Sakata N, Iwagami M, Tamiya N, Akishita M, Yamanaka T. National trends in gastrostomy in older adults between 2014 and 2019 in Japan. *Geriatr Gerontol Int*. 2022;22(8):648-652.
 11. Hidaka R, Masuda Y, Ogawa K, Tanaka T, Kanazawa M, Suzuki K, Stading M, Iijima K, Matsuo K. Impact of oral frailty prevention program with textured lunch gatherings on attitude and behavior towards eating habits and improving oral frailty: The Comprehensive Awareness Modification of Mouth, Chewing And Meal (CAMCAM) program. *Preprint from Research Square*, 02 Mar 2023, doi: 10.21203/rs.3.rs-2604863/v1 PPR: PPR624235
 12. Hosoi T, Yakabe M, Sasakawa H, Sasako T, Ueki K, Kato S, Tokuoka SM, Oda Y, Abe M, Matsumoto T, Akishita M, Ogawa S. Sarcopenia phenotype and impaired muscle function in male mice with fast-twitch muscle-specific knockout of the androgen receptor. *Proc Natl Acad Sci USA*. 2023;120(4):e2218032120.
 13. Hosoi T, Yamana H, Tamiya H, Matsui H, Fushimi K, Akishita M, Yasunaga H, Ogawa S. Association between comprehensive geriatric assessment and polypharmacy at discharge in patients with ischaemic stroke: a nationwide retrospective cohort study. *EclinicalMedicine* 50: 101528,2022
 14. Ide H, Akehi Y, Fukuhara S, Ohira S, Ogawa S, Kataoka T, Kumagai H, Kobayashi K, Komiya A, Shigehara K, Syuto T, Soh J, Tanabe M, Taniguchi H, Chiba K, Matsushita K, Mitsui Y, Yoneyama T, Shirakawa T, Fujii Y, Kumano H, Ueshiba H, Amano T, Sasaki H, Maeda S, Mizokami A, Suzuki K, Horie S. Summary of the Clinical Practice Manual for Late-Onset Hypogonadism. *Int J Urol* 2023. doi: 10.1111/iju.15160. Online ahead of print.
 15. Iki M, Fujimori K, Nakatoh S, Tamaki J, Ishii S, Okimoto N, Ogawa S. Guideline adherence by physicians for management of glucocorticoid-induced osteoporosis in Japan: a nationwide health insurance claims database study. *Osteoporosis Int*. 33:1097-1108,2022
 16. Iki M, Fujimori K, Nakatoh S, Tamaki J, Ishii S, Okimoto N, Kamiya K, Ogawa S. Delayed

- initiation of anti-osteoporosis medications increases subsequent hip and vertebral fractures in patients on long-term glucocorticoid therapy: a nationwide health insurance claims database study in Japan. *Bone* 160:116396,2022
17. Iki M, Fujimoto K, Nakatoh S, Tamaki J, Ishii S, Okimoto N, Kamiya K, Ogawa S. Real-world effectiveness of anti-osteoporosis medications for the prevention of incident hip and clinical vertebral fractures in patients on long-term glucocorticoid therapy: a nationwide health insurance claims database study in Japan. *Bone* 166:116605,2023
 18. Imoto S, Suzukawa M, Takeda K, Motohashi T, Nagase M, Enomoto Y, Kawasaki Y, Nakano E, Watanabe M, Shimada M, Takada K, Watanabe S, Nagase T, Ohta K, Teruya K, Nagai H. Evaluation of tuberculosis diagnostic biomarkers in immunocompromised hosts based on cytokine levels in QuantiFERON-TB Gold Plus. *Tuberculosis (Edinb)*. 2022;136:102242.
 19. Imoto S, Suzukawa M, Takada K, Watanabe S, Igarashi S, Kitani M, Nagase T, Ohta K. Immunoglobulin A promotes IL-6 and IL-8 production, proliferation, and migration by the human bronchial smooth muscle cells. *Cell Immunol*. 2022;381:104612.
 20. Ishii M, Yamaguchi Y, Hamaya H, Iwata Y, Takada K, Ogawa S, Imura M, Akishita M. Influence of oral health on frailty in patients with type 2 diabetics aged 75 years or older. *BMC Geriatr*. 22:145,2022
 21. Iwasaki M, Ohara Y, Motokawa K, Hayakawa M, Shirobe M, Edahiro A, Watanabe Y, Awata S, Okamura T, Inagaki H, Sakuma N, Obuchi S, Kawai H, Ejiri M, Ito K, Fujiwara Y, Kitamura A, Nofuji Y, Abe T, Iijima K, Tanaka T, Son BK, Shinkai S, Hirano H. Population-based reference values for tongue pressure in Japanese older adults: a pooled analysis with over 5,000 participants. *J Prosthodont Res*. 2023;67(1):62-69, doi:10.2186/jpr.JPR_D_21_00272.
 22. Kasajima M, Kusaka S, Matsui H, Tanaka T, Son BK, Iijima K, Goda K, Kitsuregawa M, Eggleston K, Bhattacharya J, Hashimoto H. Frailty and dementia in Japan's ageing population: projected needs and economic costs of care. *The Lancet public health*. 2022;7(5):e458-e468, doi: 10.1016/S2468-2667(22)00044-5.
 23. Kasajima M, Eggleston K, Kusaka S, Matsui H, Tanaka T, Son BK, Iijima K, Goda K, Kitsuregawa M, Bhattacharya J, Hashimoto H. Projecting prevalence of frailty and dementia and the economic cost of care in Japan from 2016 to 2043: a microsimulation modelling study. *Lancet Public Health*. 2022 May;7(5):e458-e468, doi: 10.1016/S2468-2667(22)00044-5.
 24. Kobayashi A, Azuma K, Takeiwa T, Kitami T, Horie K, Ikeda K, Inoue S. A FRET-based respirasome assembly screen identifies spleen tyrosine kinase as a target to improve muscle mitochondrial respiration and exercise performance in mice. *Nat Commun*. 2023;14(1):312. doi: 10.1038/s41467-023-35865-x.
 25. Kojima T, Hamaya H, Ishii S, Hattori Y, Akishita M. Association of disability level with polypharmacy and potentially inappropriate medication in community dwelling older people. *Arch Gerontol Geriatr*. 2023 Mar;106:104873.
 26. Konno D, Ikegaya Y, Sasaki T. Weak representation of awake/sleep states by local field potentials in aged mice. *Sci Rep*. 12:7766, 2022
 27. Lyu W, Tanaka T, Son BK, Yoshizawa Y, Akishita M, Iijima K. Associations of nutrition-related, physical, social factors and their combinations with sarcopenia in community-dwelling older adults: Kashiwa Cohort Study. *Nutrients*. 2022; 14(17): 3544. doi: 10.3390/nu14173544.
 28. Lyu W, Tanaka T, Son BK, Akishita M, Iijima K. Associations of multi-faceted factors and their combinations with frailty in Japanese community-dwelling older adults: Kashiwa cohort study. *Arch Gerontol Geriatr*. 2022;102:104734. doi: 10.1016/j.archger.2022.104734.
 29. Mizumoto J, Son D, Izumiya M, Horita S, Eto M. Experience of residents learning about social determinants of health and an assessment tool: Mixed-methods research. *J Gen Med*. 2022;00:1-8. doi: 10.1002/jgf2.559.
 30. Mizumoto J, Mitsuyama T, Kumagaya S, Eto M, Izumiya M, Horita S. Primary care nurses during the coronavirus disaster and their struggle: Qualitative research. *J Gen Fam Med*. 2022. doi: 10.1002/jgf2.566.

31. Mizumoto J, Mitsuyama T, Kondo S, Izumiya M, Horita S, Eto M. Defining the observable processes of patient care related to social determinants of health. *Med Educ*. 2022 Aug 11. doi: 10.1111/medu.14915.
32. Mori H, Izumiya M, Hayashi M, Eto M. Current perception of social accountability of medical schools in Japan: A qualitative content analysis. *Med Teach*. 2022;Nov2:1-8.
33. Mori T, Wakabayashi H, Kishima M, Itoda M, Fujishima I, Kunieda K, Ohno T, Shigematsu T, Oshima F, Ogawa N, Nishioka S, Momosaki R, Shimizu A, Saito Y, Yamada M, Ogawa S. Association between inflammation and functional outcome in patients with sarcopenic dysphagia. *J Nutr Health Aging* 26:400-406,2022
34. Moritoyo T, Nishimura N, Hasegawa K, Ishii S, Kirihara K, Takata M, Kishi SA, Umeda-Kameyama Y, Kawarasaki S, Ihara R, Sakanaka C, Wakabayashi Y, Niizuma K, Tominaga T, Yamazaki T, Hasumi K. A first-in-human study of the anti-inflammatory profibrinolytic TMS-007, an SMTP family triphenyl phenol. *Br J Clin Pharmacol*. 2022 Dec 23. doi: 10.1111/bcp.15651. Online ahead of print.
35. Nagatani M, Tanaka T, Son BK, Kawamura J, Tagomori J, Hirano H, Shirobe M, Iijima K. Oral Frailty as a Risk Factor for Mild Cognitive Impairment in Community-Dwelling Older Adults: Secondary Analysis of the Kashiwa Study Data. *Exp Gerontol*. 2023;172:112075. doi:10.1016/j.exger.2022.112075
36. Nakatoh S, Fujimori K, Ishii S, Tamaki J, Okimoto N, Ogawa S, Iki M. Association of pharmacotherapy with the second hip fracture incidence in women: a retrospective analysis of the National Database of Health Insurance Claims and Specific Health Checkups of Japan. *Geriatr. Gerontol. Int*. 22:930-937,2022
37. Nakatoh S, Fujimori K, Ishii S, Tamaki J, Okimoto N, Ogawa S, Iki M. Association between pharmacotherapy and secondary hip fracture in a real-world setting: a nationwide database study. *J Bone Miner Metab*. 41:248-257,2023
38. Nishimoto M, Tanaka T, Hirano H, Watanabe Y, Oharav Y, Shirobe M, Iijima K. Severe periodontitis increases the risk of oral frailty: A six-year follow-up study from Kashiwa cohort study. *Geriatrics (Basel)*. 2023;8(1):25, doi: 10.3390/geriatrics8010025.
39. Nishioka S, Fujishima I, Kishima M, Ohno T, Shimizu A, Shigematsu T, Itoda M, Wakabayashi H, Kunieda K, Ohshima F, Ogawa S, Fukuma K, Ogawa N, Kayashita J, Yamada M, Mori T, Onizuka S. Association of existence of sarcopenia and poor recovery of swallowing function in post-stroke patients with severe deglutition disorder: A multicenter cohort study. *Nutrients* 14:4115,2022
40. Nishita Y, Makizako H, Jeong S, Otsuka, R, Kim H, Obuchi S, Fujiwara Y, Ohara Y, Awata S, Yamada M, Iijima K, Shimada H, Suzuki T. Temporal trends in cognitive function among community-dwelling older adults in Japan: Findings from the ILSA-J integrated cohort study. *Arch Gerontol Geriatr*. 2022 Sep-Oct;102:104718, doi: 10.1016/j.archger.2022.104718.
41. Nomura K, Ebihara S, Ikebata Y, Umegaki H, Ooi K, Ogawa S, Katsuya T, Kobayashi Y, Sakurai T, Miyao M, Yamaguchi K, Akishita M, The Japan Geriatrics Society Geriatric Medical Practice Committee. Japan Geriatrics Society “Statement for the Use of Telemedicine in Geriatric Care-Telemedicine as a Complement to In-person Medical Practice”: Geriatric Medical Practice Committee consensus statement. *Geriatr. Gerontol. Int*. 22:913-916,2022
42. Sakai K, Nakayama E, Yoneoka D, Sakata N, Iijima K, Tanaka T, Hayashi K, Sakuma K, Hoshino E. Association of Oral Function and Dysphagia with Frailty and Sarcopenia in Community-Dwelling Older Adults: A Systematic Review and Meta-Analysis. *Cells*. 2022 Jul 14; 11(14):2199, doi: 10.3390/cells11142199.
43. Sato S, Miyazaki S, Tamaki A, Yoshimura Y, Arai H, Fujiwara D, Katsura H, Kawagoshi A, Kozu R, Maeda K, Ogawa S, Ueki J, Wakabayashi H. Respiratory sarcopenia: A position paper by four professional organizations. *Geriatr. Gerontol. Int*. 23:5-15,2023
44. Son BK, Imoto T, Inoue T, Nishimura T, Lyu W, Tanaka T, Iijima K. Different reversibility of skeletal muscle mass and strength in elderly Japanese women after the first wave of COVID-19.

- JCSM rapid communication* 2023 Feb 27. DOI:10.1002/rco2.73. Online ahead of print
45. **Son BK, Imoto T, Inoue T, Nishimura T, Tanaka T, Iijima K.** Social detachment influenced muscle mass and strength during the COVID-19 pandemic in Japanese community-dwelling older women *J Frailty Aging* 2022;11(2):231-235. doi:10.14283/jfa.2022.4
 46. **Sun Y, Iwagami M, Sakata N, Ito T, Inokuchi R, Uda K, Hamada S, Ishimaru M, Komiyama J, Kuroda N, Yoshie S, Ishizaki T, Iijima K, Tamiya N.** Development and validation of a risk score to predict the frequent emergency house calls among older people who receive regular home visits. *BMC Primary Care*. 2022.5;23(132).
 47. **Suzuki Y, Shiraishi N, Komiya H, Sakakibara M, Akishita M, Kuzuya M.** Potentially inappropriate medications increase while prevalence of polypharmacy/hyperpolypharmacy decreases in Japan: A comparison of nationwide prescribing data. *Arch Gerontol Geriatr*. 2022;102:104733.
 48. **Takahashi K, Tanaka T, Yoshizawa Y, Fujisaki-Sueda-Sakai M, Son BK, Iijima K.** Lower urinary tract symptoms and functional ability in older adults: A community-based cross-sectional study. *BMC open* 2022; 12(4): e054530. doi: 10.1136/bmjopen-2021-054530.
 49. **Takase M, Takahashi K, Ogino R, Nitani R, Tanaka T, Saisho S, Goto J, Iijima K.** Functional capacity in community-dwelling older adults maintained by a higher friend network than family network: Implications from a two-year longitudinal study. *BMC Res Notes*, 2022 Oct 11;15(1):319, doi: 10.1186/s13104-022-06216-8.
 50. **Tamaki J, Ogawa S, Fujimori K, Ishii S, Nakatoh S, Okimoto N, Kamiya K, Iki M.** Hip and vertebral fracture risk after initiating anti-diabetic drugs in Japanese elderly: a nationwide study. *J Bone Miner Metab*. 41:29-40,2023
 51. **Tanaka T, Yoshizawa Y, Sugaya K, Yoshida M, Son BK, Lyu W, Tsushita K, Iijima K.** Predictive validity of the Questionnaire for Medical Checkup of Old-Old for functional disability: using the National Health Insurance Database System. *Geriatr Gerontol Int*. 2023. doi: 10.1111/ggi.14533.
 52. **Tanaka T, Son BK, Iijima K.** Poor health behaviors among housebound Japanese community-dwelling older adults due to prolonged self-restraint during the first COVID-19 pandemic: A cross-sectional survey. *J Frailty Aging* 2023;12(1):86-90. doi: 10.14283/jfa.2022.20.
 53. **Tanaka T, Son BK, Lyu W, Iijiam K.** The impact of social engagement on the development of sarcopenia among community-dwelling older adults: A Kashiwa cohort study. *Geriatr Gerontol Int* 2022;22(5):384-391. doi: 10.1111/ggi.14372.
 54. **Wakabayashi H, Kishima M, Itoda M, Fujishima I, Kunieda K, Ohno T, Shigematsu T, Oshima F, Mori T, Ogawa N, Nishioka S, Momosaki R, Yamada M, Ogawa S.** Prevalence of hoarseness and its association with severity of dysphagia in patients with sarcopenic dysphagia. *J. Nutr Health Aging* 26:266-271,2022
 55. **Watanabe S, Kobayashi K, Suzukawa M, Igarashi S, Takada K, Imoto S, Kitani M, Fukami T, Nagase T, Ohta K.** Identification of ANXA2 on epithelial cells as a new receptor for secretory IgA using immunoprecipitation and mass spectrometry. *Clin Exp Immunol*. 2022;208(3): 351-360
 56. **Yamamoto K, Akasaka H, Yasunobe Y, Shimizu A, Nomoto K, Nagai K, Umegaki H, Akasaki Y, Kojima T, Kozaki K, Kuzuya M, Ohishi M, Akishita M, Takami Y, Rakugi H; Cherry Study Group.** Clinical characteristics of older adults with hypertension and unrecognized cognitive impairment. *Hypertens Res*. 2022;45(4):612-619.
 57. **Yamamoto T, Tanaka T, Hirano H, Mochida Y, Iijima K.** Model to Predict Oral Frailty Based on Questionnaire: A Cross-Sectional Study. *Int J Environ Res Public Health*. 2022 Oct 14;19(20): 13244, doi: 10.3390/ijerph192013244.
 58. **Yamanaka T, Kidana K, Yamaguchi Y, Hirahara S, Hirakawa Y, Mizuki M, Arai H, Akishita M, Miura H.** Palliative home care for older patients with respiratory disease in Japan: Practices and opinions of physicians. *Geriatr Gerontol Int*. 2022;22(11):943-949.
 59. **Yakabe M, Hosoi T, Sasakawa H, Akishita M, Ogawa S.** Kampo formula Hochu-ekki-to (Bu-Zhong-Yi-Qi-Tang, TJ-41) ameliorates muscle atrophy by modulating atrogenes and AMPK in

vivo and in vitro. *BMC Complement Med Ther.* 22:341,2022

60. **Yakabe M, Shibasaki K, Hosoi T, Matsumoto S, Hoshi K, Akishita M, Ogawa S.** Validation of the questionnaire for medical checkup of old-old (QMCOO) score cutoff to diagnose frailty. *BMC Geriatr.* 23:157,2023
61. **Yakabe M, Shibasaki K, Hosoi T, Matsumoto S, Hoshi K, Akishita M, Ogawa S.** Effectiveness of the questionnaire for medical checkup of old-old (QMCOO) to diagnose frailty in community-dwelling elderly adults. *Geriatr. Gerontol. Int.* 22: 127-131,2022
62. **Yoshizawa Y, Tanaka T, Takahashi K, Fujisaki M, Son BK, Iijima K.** Impact of Health Literacy on the Progression of Frailty after 4 Years among Community-Dwelling Older Adults. *Int J Environ Res Public Health.* 2022;19(1):394.

Surgical Sciences

1. Surgery

Department of Thoracic Surgery

Professor

Sato, Masaaki

Lecturer

Konoeda, Chihiro

Kawashima, Mitsuaki

Assistant Professor

Nagano, Masaaki

Nakao, Keita

Cong, Yue

Muraoka, Tatsuya

Homepage <https://plaza.umin.ac.jp/~ctstokyo/thoracic/index.html>

History

Study on thoracic surgery has begun since 1916 when symposium on lung surgery was held at annual meeting of Japan Surgical Society. Clinical and basic research of the thoracic surgery have been performed since the prewar era at the Second department of Surgery in this university. Professor Tsuduki, Masao adopted the modified Coryllos's thoracoplasty for the treatment of the pulmonary tuberculosis in 1934. In 1942, they initiated thoracoscopy for the treatment of the tuberculosis in our country. Before the World War II, thoracic surgery had been performed under spontaneous breathing. Since 1950 safer anesthesia with endotracheal intubation has been started in this university.

After the successful application of the antituberculosis drugs, surgical treatment of the thoracic malignant neoplasms was the major concern of the thoracic surgery. Case reports on surgical therapy for lung cancer has been present since 1920's in our country. In 1950, successful right pneumonectomy for the primary lung cancer in this university was reported. Surgical therapy for the mediastinal tumor was also begun in 1950. In 1954,

thymectomy through median sternotomy has begun in our department.

The Department of Cardiothoracic Surgery, The University of Tokyo, was established on December 15, 1964, as the first department of this field along with the cardiovascular surgery in the Japanese national universities. It has played an internationally leading role and contributed to development of the field in our country.

Professors and Chairs in the history of the department are as follows: Kimoto, Seiji (1964.12.15 ~ 1968.3.31), Saigusa, Masahiro (1968.4.1 ~ 1981.3.31), Asano, Ken-ichi (1981.4.1 ~ 1986.3.31), Furuse, Akira (1986.4.1 ~ 1997.3.31) and Takamoto, Shinichi (1997.6.1 ~ 2009.3.31).

The Department of Cardiothoracic Surgery has been divided into two departments, Department of Cardiovascular Surgery and Department of Thoracic Surgery in 1995. The mission of the Department of Thoracic Surgery is to cure the patients with diseases of the thoracic organs through clinical works, basic and clinical research, and education of the medical students, postgraduates, and the surgical residents in our university.

Nakajima, Jun took over the mission of the department of thoracic surgery as an independent department for the first time since April 2011 until the end of March, 2023. Sato, Masaaki has taken over the department since August 2023.

Clinical activities

Six staffs (Sato M, Konoeda C, Kawashima M, Nagano M, and Nakao K, Cong Y), who are certificated as members of the Japanese Board of General Thoracic Surgery, are in charge of the Department of Thoracic Surgery, University of Tokyo Hospital. They specialize in surgical treatment for diseases of the respiratory and the mediastinal organs and the chest wall, except for diseases of the esophagus and mammary glands.

Lung cancer is the leading cause of cancer death in our country: In 2020, Ministry of Health, Labour and Welfare documented that number of deaths from malignant neoplasms was approximately 390 thousand out of 1.37 million total deaths in Japan. Of them, 76 thousand people were killed by malignant tracheal / pulmonary neoplasms. Surgical therapy for non-small cell lung cancer (NSCLC) is thus the most important issue in our department. By the practice of treatment based on EBM, we perform basic training of thoracic surgery for medical school students, graduate students and clinical residents, as well as doing the professional education for training physicians who wish to become board-certified thoracic surgeons.

We have performed video-assisted thoracoscopy for the diagnosis and treatment of the thoracic disease with less surgical invasiveness since 1992 for safer treatment of older patients with cardiovascular and/or respiratory complications. We currently conduct a standard surgery for clinical stage I non-small cell lung cancer (NSCLC), that is, lobectomy and lymphadenectomy through thoracoscopy: Since 2015, more than 90% of patients with NSCLC has undergone thoracoscopic surgery in our department. Research on less-invasiveness, oncological advantage of the thoracoscopic surgery is thus actively done. Robot-assisted lobectomy/segmentectomy with Da Vinci has applied to lung cancer patients since January 2021.

Pulmonary metastasis represents far advanced malignant neoplasms of extrathoracic organs. Pulmonary resection is an option for the treatment of pulmonary metastasis. We actively perform pulmonary resection through thoracoscopy on patients with pulmonary metastasis who are eligible for surgical therapy through thoracoscopy

Thymic epithelial neoplasms, such as thymoma and thymic carcinoma, show broad spectrum in the degree of malignancy. They also associated with paraneoplastic syndromes, such as the myasthenia gravis and the pure red cell aplasia. Although they are relatively rare diseases, we sought to establish the strategies on diagnosis and treatment of these diseases, which are still yet to be determined, from our clinical experiences of more than 200 cases with the diseases in our department. We are now actively participating a multiinstitutional study on malignant thymic epithelial neoplasms database led by Japanese Association for research on the thymus (JART).

Our hospital has been certified as a lung transplant centers since March 2014. We have started to register patients who are eligible for lung transplantation. We successfully performed the first case in Tokyo of living donor lung transplantation in April 2015: The patients had suffered from the interstitial pneumonia. In July 2015, we also succeeded in performing brain-dead donor bilateral lung transplantation on a patient who had suffered from the pulmonary hypertension. We have performed 177 lung transplants (including 27 living related donor lung transplantations) by the end of 2023.

Academic education

Medical students in the fifth grade have three-week program on the clinical training of the thoracic and the cardiovascular surgery. They are also able to participate the clinical clerkship of the thoracic surgery, an elective course for 4 weeks. We also conduct a further research training for medical students who like to study thoracic surgery. The Department of Thoracic Surgery also offers the 4-year postgraduate program for qualified surgeons who are willing to specialize in the thoracic surgery. We have a training program for surgeons who wish to be a board-certified thoracic surgeon after 4-year residency.

Current research

Main subjects of current research at present include basic and clinical studies on the malignant neoplasms in the thorax including lung cancer and thymic tumors, and transplantation of the thoracic organs. The following items are the major themes under research in our department:

- (1) Minimally invasive surgeries for thoracic malignant neoplasms.
- (2) Navigation techniques for finding out small pulmonary lesions through thoracoscopy.
- (3) Imaging analysis of lung adenocarcinoma
- (4) Global analysis of oncogenes and suppressor genes associated with lung cancer.
- (5) Application of new fluorescent agents for diagnosis of lung cancer.
- (6) Immunotherapy for lung cancer.
- (7) Analysis on mechanisms of acute or chronic rejection of the allogeneic lung after allogeneic transplantation.
- (8) Long-term digital monitoring of post-lung transplant patients
- (9) Research on extracorporeal membranous oxygenation for bridge use to lung transplantation

Selected publications (2023)

1. Cong Y, Nagano M, Sato M. A case of *Aspergillus* empyema successfully treated by a single-stage cavernostomy and a covering procedure using both fat pad and muscle flap. *Gen Thorac Cardiovasc Surg Cases*. 2023; 2(1):91.
2. Iida T, Nagayama K, Kitano K, Yamauchi H, Ono M, Nakajima J. Modified Ravitch procedure for pectus excavatum in Marfan syndrome with annuloaortic ectasia. *Interdiscip Cardiovasc Thorac Surg*. 2023;36(6).
3. Iida T, Shimada Y, Sato M. Management and mindset for air leak and intraoperative bleeding in thoracic surgery. *J Thorac Dis*. 2023;15(8): 4137-40.
4. Ikeda T, Ichiba S, Sasaki T, Sato M, Konoeda C, Okamoto T, et al. A case of severe respiratory failure due to interstitial pneumonia successfully bridged to lung transplantation from a brain-dead

donor using 109-day veno-arterial extracorporeal membrane oxygenation. *J Artif Organs*. 2023; 26(1):84-8.

5. Ishide T, Nishi H, Miyano S, Hirakawa Y, Honda K, Abe H, et al. Kidney Podocyte Zebra Bodies after Lung Transplantation for Lymphangioleiomyomatosis. *Intern Med*. 2023;62(13):1965-70.
6. Ishii S, Minatsuki S, Hatano M, Saito A, Yagi H, Shimbo M, et al. The ratio of TAPSE to PASP predicts prognosis in lung transplant candidates with pulmonary arterial hypertension. *Sci Rep*. 2023;13(1):3758.
7. Matsumoto Y, Kage H, Morota M, Zokumasu K, Ando T, Maemura K, et al. Integrin alpha 2 is associated with tumor progression and postoperative recurrence in non-small cell lung cancer. *Jpn J Clin Oncol*. 2023;53(1):63-73.
8. Miki Y, Yamashita H, Nakajima J, Karasaki T, Kitano K, Katano A, et al. Retrospective comparison between definitive stereotactic body radiotherapy and radical surgery for 538 patients with early-stage non-small cell lung cancer in a single institution. *J Cancer Res Ther*. 2023; 19(5):1350-5.
9. Nagano M, Sato M. Impact of surgical margin after sublobar resection of lung cancer: a narrative review. *J Thorac Dis*. 2023;15(10): 5750-9.
10. Nagano M, Sato M. Ten-Year Outcome and Development of Virtual-Assisted Lung Mapping in Thoracic Surgery. *Cancers (Basel)*. 2023;15(7).
11. Nagano M, Sato M, Yanagiya M, Nakao K, Konoeda C, Kitano K, et al. Number of dye marks required in virtual-assisted lung mapping. *Gen Thorac Cardiovasc Surg*. 2023;71(5):313-20.
12. Nakajima J. Minimally Invasive Thymectomy Could Be Attempted for Locally Advanced Thymic Malignancies: A Real-World Study With Propensity Score-Matched Analysis. *J Thorac Oncol*. 2023;18(5):559-60.
13. Nakajima J. Is Sublobar Resection Applicable to T1c Non-Small Cell Lung Cancer? *Ann Thorac Surg*. 2023;115(6):1351-2.
14. Nobori Y, Anraku M, Yamauchi Y, Mun M, Yoshino I, Nakajima J, et al. Risk-adjusted hazard analysis of survival after pulmonary

- metastasectomy for uterine malignancies in 319 cases. *JTCVS Open*. 2023;13:411-22.
15. Oishi H, Okada Y, Sato M, Nakajima J, Nakajima D, Shiraishi T, et al. Prognostic factors for lung transplant recipients focusing on age and gender: the Japanese lung transplantation report 2022. *Surg Today*. 2023;53(10):1188-98.
16. Okumura M, Yoshino I, Funaki S, Okuda K, Watanabe SI, Tsuboi M, et al. Long-term outcomes following surgical treatment for thymic epithelial tumor in Japan and an analysis of prognostic factors based on the Japanese Association for Research on the Thymus nationwide database. *Surg Today*. 2023;53(11):1247-59.
17. Sato C, Kubo T, Shibata E, Yanagiya M, Nakajima J, Abe O. Successful transcatheter embolization of an unruptured idiopathic peripheral pulmonary artery aneurysm. *Radiol Case Rep*. 2023;18(1):8-10.
18. Sato M. The pros and cons of uniportal VATS segmentectomy in the treatment of early-stage lung cancer: should the procedure be prioritized? *J Thorac Dis*. 2023;15(2):238-41.
19. Sun C, Nagaoka K, Kobayashi Y, Maejima K, Nakagawa H, Nakajima J, et al. Immunotherapies targeting neoantigens are effective in PD-1 blockade-resistant tumors. *Int J Cancer*. 2023;152(7):1463-75.
20. Takada J, Sato M, Konoeda C, Kaneko H, Shimada S, Hirata Y, et al. Bilateral living-related lobar lung transplantation avoiding bronchial stenosis associated with scoliosis by modified anastomosis: a case report. *Gen Thorac Cardiovasc Surg Cases*. 2023;2(1):84.
21. Tian D, Yan HJ, Shiiya H, Sato M, Shinozaki-Ushiku A, Nakajima J. Machine learning-based radiomic computed tomography phenotyping of thymic epithelial tumors: Predicting pathological and survival outcomes. *J Thorac Cardiovasc Surg*. 2023;165(2):502-16.e9.
22. Xu SJ, Chen RQ, Tu JH, You CX, Chen C, Zhang ZF, et al. Effects of a ground-glass opacity component on the recurrence and survival of pathological stage IA3 lung adenocarcinoma: a multi-institutional retrospective study. *Transl Lung Cancer Res*. 2023;12(5):1078-92.
23. Yamaguchi M, Sato M, Kitano K, Konoeda C, Nakajima J. Lung transplantation for cystic fibrosis complicated by cirrhosis: A case report. *Respir Med Case Rep*. 2023;44:101879.
24. Yamauchi Y, Nakajima J, Mun M, Shintani Y, Kuroda H, Iwata T, et al. Survival after Lung Metastasectomy from Esophageal Cancer: Results from a Multi-Institutional Database. *Cancers (Basel)*. 2023;15(5).
25. Yamaya T, Sato M, Konoeda C, Nakajima J. Living-donor lobar lung transplantation from a hepatitis B surface antigen-positive donor to a negative recipient. *BMJ Case Rep*. 2023;16(10).
26. Yanagiya M, Nagano M, Nakajima J. Fissureless technique of robotic left lingular segmentectomy for primary lung cancer with incomplete fissure: a case report. *J Cardiothorac Surg*. 2023;18(1):125.
27. Yoshida D, Kamiya M, Kawashima S, Yoshioka T, Hino H, Abe A, et al. Rapid imaging of thymoma and thymic carcinoma with a fluorogenic probe targeting γ -glutamyltranspeptidase. *Sci Rep*. 2023;13(1):3757.

Department of Cardiac Surgery

Professor

Minoru Ono, M.D., Ph.D.

Associate Professor

Yasutaka Hirata, M.D., Ph.D.

Lecturer

Haruo Yamauchi, M.D., Ph.D., Shogo Shimada, M.D., Ph.D.,

Mitsutoshi Kimura, M.D., Ph.D.

Associate

Masahiko Ando, M.D., Ph.D., Hyoe Komae, M.D., Ph.D., Tomoyuki Iwase, M.D., Ph.D.,

Miyuki Shibata, M.D., Ph.D., Yangsin Lee, M.D., Ph.D., Takayuki Gyoten, M.D. Ph.D.,

Homepage <http://cts.m.u-tokyo.ac.jp/>

Introduction and Organization

Cardiac surgery in the Department was initiated by Dr. Seiji Kimoto, who performed ligation of patent ductus arteriosus in June, aortic arch aneurysm resection in July and first-in-Japan Blalock-Taussig operation for Tetralogy of Fallot in October in 1951. He also started implantation of alcohol-preserved aortic homograft for abdominal aortic aneurysm in 1952, and closed commissurotomy for mitral valve stenosis in 1954. The first open heart surgery (atrial septal defect closure) was performed in 1955, using selective brain perfusion cooling method that was developed in the Department.

Establishment of Department of Thoracic Surgery in the University of Tokyo Hospital was approved by the government first in Japan December 15, 1964. Under the leadership of Professor Kimoto excellent research works were created especially on pacemaker and artificial heart, and many opinion leaders were produced. Dr. Masahiro Saigusa, the second Professor, endeavored to make open heart surgery safer by introducing new-generation heart-lung machines to the Department. Dr. Kenichi Asano, the third Professor, started posterior-leaflet preserving mitral valve

replacement first in Japan. He also dramatically improved surgical results of Tetralogy of Fallot. Dr. Akira Furuse, the fourth Professor, modernized management of extremely busy clinical works. During this time, the Department was divided into two Divisions, Cardiovascular and General thoracic, due to the University policy of Graduate-school.

Dr. Shinichi Takamoto assumed the fifth Professor in June 1997. He rearranged clinical teams into three groups (adult cardiac disease, thoracic aortic disease and congenital heart disease) to adapt the rapid progress of cardiovascular surgery.

Dr. Minoru Ono was elected as the sixth Professor in November 2009. Advanced Heart Failure Center was open on the 5th Floor of Hospital Building B, January 2018 to cope with an increasing number of patients who require ventricular assist device and heart transplantation treatment. Present staffs are one Chief Professor, one Associate Professor and three Lecturer and seven Associates.

Clinical Activities

Clinical conference starts at 7:15 am in weekdays. Regular surgery is scheduled on every weekday. Adult

patients are hospitalized in the South Wing of 5th floor, and pediatric patients in the South Wing of 2nd floor. Clinics are open Monday through Friday for the follow-up visit as well as for patient referral.

Case volume in recent years has been over 400, which is one of the highest in Japan. We are leading in Japan by showing excellent surgical results. There are 10 Board-certified cardiovascular surgeons, each of whom has his own subspecialty among adult cardiac, thoracic aortic or congenital heart disease. We are famous for off-pump coronary artery bypass surgery, mitral valve plasty, heart transplantation, ventricular assist device implantation, aortic valve sparing root replacement, arch replacement, treatment of extended thoracic aortic aneurysm and repair of complex congenital heart diseases, such as Jatene, Fontan and Norwood operations. Transcatheter aortic valve replacement was initiated in 2015. Many high-risk very old patients with aortic valve stenosis were successfully treated.

The University of Tokyo Tissue Bank was founded in 1997, based on the Department of Cardiovascular Surgery. The Bank has been actively promoting procurement, preservation and shipping of human valve and blood vessel allograft in Japan. We take the lead in surgical treatment using allograft for severe active endocarditis or infection of aortic aneurysm or vascular prosthesis. Surgical treatment using allograft was approved for health insurance coverage by the Government in 2018. As of March 2024, 219 cases of heart transplantation including 16 pediatric patients and 432 cases of ventricular assist device (VAD) implantation including 292 implantable continuous-flow VADs were performed in The University Hospital with excellent long-term survival.

Teaching Activities

We have the chair of systematic review of cardiovascular surgery in the spring term at the 2nd grade of medical course. We expose the students to daily clinical works as well as research works during the course of “Free Quarter” and “Research Lab Visit”, which are scheduled in the summer and spring vacations at 1st and 2nd grade. Joint lectures with the Cardiology Department are scheduled 3rd through 4th grades. Each student is assigned one or two cardiovascular surgical

cases in the Regular Clinical Clerkship, in which he/she is required to learn preoperative patient evaluation and management, surgical treatment and postoperative care, based on participatory practice. There are also fifteen small key-lectures on cardiovascular surgery. Hands-on practice is provided during the Advanced Clinical Clerkship one-month course in the last months of 3rd grade.

We take charge in core surgical curriculum in the “Super-rotation” postgraduate training. We offer a program in which each resident can learn basic knowledge of cardiovascular disease and surgery, and hemodynamic and respiratory evaluation as well as basic surgical techniques and patient management. Residents who take the course of cardiovascular surgery are required three-year general surgical training for General Surgery Board certification. We have well-developed specialty/subspecialty training programs to allow the residents to pass Cardiovascular Board Examination by 9-10th postgraduate year.

Research Activities

In order to achieve excellent clinical results and to seek for new possibilities of surgical treatments, it is essential for cardiothoracic surgical department of the University to have active research programs in clinical and basic subjects. The Cardiothoracic Department of the University of Tokyo has created highly active research programs in the every field of cardiothoracic surgery, played an internationally leading role and contributed to its development. A research meeting is held once a month on a research project for every member of the department to understand and to make free thorough discussions of the subject.

Basic and/or clinical research activities are focused on 1) establishment of recovery and weaning protocols of left ventricular assist device, 2) basic and clinical research on cryopreserved allograft, 3) application of regenerative medicine to end-stage heart failure, 4) analysis of cardiomyocytes matured and differentiated from iPS cells, 5) mechanism analysis of right heart failure and development of effective pharmacological and mechanical therapy, 6) development of versatile suture device, 7) clinical research to test the safety and efficacy of artificial pancreas during open heart surgery.

References

1. Gyoten T, Amiya E, Kinoshita O, Tsuji M, Kimura M, Hatano M, Ono M. Clinical outcomes of continuous flow left ventricular assist device therapy as bridge to transplant strategy in muscular dystrophy: a single-center study. *Gen Thorac Cardiovasc Surg*. 2023 Jun;71(6):347-353. PMID: 36348232.
2. Takura T, Ono M, Ako J, Ikari Y, Toda K, Sawa Y; ETICA Study Investigators. Clinical and Economic Evaluation of Impella Treatment for Fulminant Myocarditis - A Preliminary Retrospective Cohort Study in Japan. *Circ J*. 2023 Apr 25;87(5):610-618. PMID: 36418111.
3. Gomes WJ, Dayan V, Myers PO, Almeida R, Puskas JD, Taggart DP, Arai H, Ono M, Okita Y, Yadava OP, Kim KB, Zheng Z, Rodriguez-Roda J, Parolari A, Uva MS, Sádaba JR. The 2021 American College of Cardiology/American Heart Association/Society for Cardiac Angiography and Interventions guideline for coronary artery revascularization. A worldwide call for consistency and logic. *J Thorac Cardiovasc Surg*. 2023 Jan;165(1):164-167. PMID: 36522806.
4. Takura T, Komuro I, Ono M. Trends in the cost-effectiveness level of percutaneous coronary intervention: Macro socioeconomic analysis and health technology assessment. *J Cardiol*. 2023 Apr;81(4):356-363. PMID: 36182005.
5. Ikeda Y, Ako J, Toda K, Hirayama A, Kinugawa K, Kobayashi Y, Ono M, Nishimura T, Sato N, Shindo T, Takayama M, Yasukochi S, Shiose A, Sawa Y; J-PVAD Investigators. Short-Term Outcomes of Impella Support in Japanese Patients With Cardiogenic Shock Due to Acute Myocardial Infarction - Japanese Registry for Percutaneous Ventricular Assist Device (J-PVAD). *Circ J*. 2023 Apr 25;87(5):588-597. PMID: 36682787.
6. Hasegawa H, Shinya Y, Ono M, Kikuta S, Kondo K, Saito N. Kashimé: A Novel Knotless Surgical Suture to Simplify Dural Stitches in Endoscopic Transnasal Surgery. *Oper Neurosurg (Hagerstown)*. 2023 Apr 1;24(4):417-424. PMID: 36701657.
7. Gyoten T, Ono M. Outcomes of continuous flow left ventricular assist device after surgical left ventricular restoration. *Gen Thorac Cardiovasc Surg*. 2023 Aug;71(8):480-486. PMID: 36810746.
8. Yamada T, Nomura S, Amiya E, Katoh M, Inoue S, Hatsuse S, Fujita K, Ito M, Fujita T, Bujo C, Tsuji M, Ishida J, Ko T, Yamada S, Katagiri M, Sassa T, Kinoshita O, Nawata K, Tobita T, Satoh M, Ishiwata J, Daimon M, Tatsuno K, Fukuda S, Kashimura T, Minamino T, Hatano M, Ono M, Aburatani H, Komuro I. LMNA Mutations and Right Heart Failure in Cardiomyopathy Patients With Left Ventricular Assist Devices. *J Card Fail*. 2023 May;29(5):855-857. PMID: 36871612.
9. Imamura T, Kinugawa K, Nishimura T, Toda K, Saiki Y, Niinami H, Nunoda S, Matsumiya G, Nishimura M, Arai H, Yanase M, Fukushima N, Nakatani T, Shiose A, Shibasaki I, Sakata Y, Ono M; J-MACS Investigators. Novel Scoring System to Risk Stratify Patients Receiving Durable Left Ventricular Assist Device From J-MACS Registry Data. *Circ J*. 2023 Jul 25;87(8):1103-1111. PMID: 37258218.
10. Iida T, Nagayama K, Kitano K, Yamauchi H, Ono M, Nakajima J. Modified Ravitch procedure for pectus excavatum in Marfan syndrome with annuloaortic ectasia. *Interdiscip Cardiovasc Thorac Surg*. 2023 Jun 1;36(6):ivad095. PMID: 37307071.
11. Tsuji S, Shimada S, Ono M. Modified Heterotopic Abdominal Heart Transplantation and a Novel Aortic Regurgitation Model in Rats. *J Vis Exp*. 2023 Jun 2;(196). PMID: 37335093.
12. Kakuda N, Amiya E, Hatano M, Ishida J, Tsuji M, Bujo C, Yagi H, Fujita K, Ishii S, Isotani Y, Kurihara T, Numata G, Gyoten T, Shimada S, Ando M, Ono M, Komuro I. Effect of renal function under left ventricular assist device support on the cardiac function and clinical events after heart transplantation. *Clin Transplant*. 2023 Dec;37(12):e15107. PMID: 37615650.
13. Inoue S, Ko T, Nomura S, Yamada T, Zhang B, Dai Z, Jimba T, Kato M, Ishida J, Amiya E, Hatano M, Takeda N, Morita H, Ono M, Komuro I. Compound Heterozygous Truncating Variants in the *BAG5* Gene As a Cause of Early-Onset Dilated Cardiomyopathy. *Circ Genom Precis Med*. 2023 Dec;16(6):e004282. PMID: 37873655.

14. Tanaka S, Nishinaka T, Umeki A, Murakami T, Imaoka S, Mizuno T, Tsukiya T, Ono M. Hemodynamic Evaluation of Asynchronous Speed Modulation of a Continuous-Flow Left Ventricular Assist Device in an Acute-Myocardial Injury Sheep Model. *Ann Biomed Eng.* 2024 Feb; 52(2):364-375. PMID: 37851145.
15. Toda K, Ako J, Hirayama A, Kinugawa K, Kobayashi Y, Ono M, Nishimura T, Sato N, Shindo T, Takayama M, Yasukochi S, Shiose A, Sawa Y. Outcomes of Venous-Arterial Extracorporeal Membrane Oxygenation With Percutaneous Left Ventricular Unloading in Fulminant Myocarditis. *ASAIO J.* 2024 Apr 1;70(4):258-263. PMID: 38029755.
16. Ito K, Sasaki K, Ono M, Suzuki T, Sakamoto K, Okamoto H, Katori N, Momose N, Araki Y, Tojo K, Ieko M, Komiyama Y, Saiki Y. Investigation of real-world heparin resistance and anticoagulation management prior to cardiopulmonary bypass: report from a nationwide survey by the Japanese Association for Thoracic Surgery heparin resistance working group. *Gen Thorac Cardiovasc Surg.* 2024 Jan;72(1):8-14. PMID: 37195584.
17. Kanno Y, Okamoto K, Shinohara T, Kinoshita O, Hatano M, Ikeda M, Harada S, Okugawa S, Moriya K, Ono M, Tsutsumi T. Pre-Transplant Seroprevalence, Associated Factors, and Post-Transplant Incidence of *Toxoplasma gondii* Infection Among Heart Transplant Recipients in Japan. *Transplant Proc.* 2024 Jan-Feb;56(1):148-152. PMID: 38177043.
18. Zhu S, Xuan J, Shentu Y, Kida K, Kobayashi M, Wang W, Ono M, Chang D. Effect of chitin-architected spatiotemporal three-dimensional culture microenvironments on human umbilical cord-derived mesenchymal stem cells. *Bioact Mater.* 2024 Feb 9;35:291-305. PMID: 38370866.
19. Takura T, Komuro I, Ono M. Trends in the cost-effectiveness level of percutaneous coronary intervention: Macro socioeconomic analysis and health technology assessment. *J Cardiol.* 2023 Apr;81(4):356-363. PMID: 36182005.
20. Bernhardt AM, Copeland H, Deswal A, Gluck J, Givertz MM; Chairs;; Co-Chairs;; Contributing Writers;; Chair;; Co-Chair;; Contributing Writers;; Chair;; Co-Chair;; Contributing Writers. The International Society for Heart and Lung Transplantation/Heart Failure Society of America Guideline on Acute Mechanical Circulatory Support. *J Heart Lung Transplant.* 2023 Apr; 42(4):e1-e64. PMID: 36805198.
21. Nagai T, Inomata T, Kohno T, Sato T, Tada A, Kubo T, Nakamura K, Oyama-Manabe N, Ikeda Y, Fujino T, Asaumi Y, Okumura T, Yano T, Tajiri K, Matsuura H, Baba Y, Sunami H, Tsujinaga S, Ota Y, Ohta-Ogo K, Ishikawa Y, Matama H, Nagano N, Sato K, Yasuda K, Sakata Y, Kuwahara K, Minamino T, Ono M, Anzai T; Japanese Circulation Society Joint Working Group. JCS 2023 Guideline on the Diagnosis and Treatment of Myocarditis. *Circ J.* 2023 Apr 25;87(5):674-754. PMID: 36908170.
22. Nomura S, Ono M. Precision and genomic medicine for dilated and hypertrophic cardiomyopathy. *Front Cardiovasc Med.* 2023 Mar 6;10:1137498. doi: 10.3389/fcvm.2023.1137498. PMID: 36950287; PMCID: PMC10025380.
23. Chang D, Yang X, Fan S, Fan T, Zhang M, Ono M. Engineering of MSCs sheet for the prevention of myocardial ischemia and for left ventricle remodeling. *Stem Cell Res Ther.* 2023 Apr 25; 14(1):102. PMID: 37098611.
24. Hiraoka E, Tanabe K, Izuta S, Kubota T, Kohsaka S, Kozuki A, Satomi K, Shiomi H, Shinke T, Nagai T, Manabe S, Mochizuki Y, Inohara T, Ota M, Kawaji T, Kondo Y, Shimada Y, Sotomi Y, Takaya T, Tada A, Taniguchi T, Nagao K, Nakazono K, Nakano Y, Nakayama K, Matsuo Y, Miyamoto T, Yazaki Y, Yahagi K, Yoshida T, Wakabayashi K, Ishii H, Ono M, Kishida A, Kimura T, Sakai T, Morino Y; Japanese Society Joint Working Group. JCS 2022 Guideline on Perioperative Cardiovascular Assessment and Management for Non-Cardiac Surgery. *Circ J.* 2023 Aug 25;87(9):1253-1337. PMID: 37558469.
25. Ogino H, Iida O, Akutsu K, Chiba Y, Hayashi H, Ishibashi-Ueda H, Kaji S, Kato M, Komori K, Matsuda H, Minatoya K, Morisaki H, Ohki T, Saiki Y, Shigematsu K, Shiiya N, Shimizu H, Azuma N, Higami H, Ichihashi S, Iwahashi T, Kamiya K, Katsumata T, Kawaharada N,

- Kinoshita Y, Matsumoto T, Miyamoto S, Morisaki T, Morota T, Nanto K, Nishibe T, Okada K, Orihashi K, Tazaki J, Toma M, Tsukube T, Uchida K, Ueda T, Usui A, Yamanaka K, Yamauchi H, Yoshioka K, Kimura T, Miyata T, Okita Y, Ono M, Ueda Y; Japanese Circulation Society, the Japanese Society for Cardiovascular Surgery, the Japanese Association for Thoracic Surgery and the Japanese Society for Vascular Surgery Joint Working Group. JCS/JSCVS/JATS/JSVS 2020 Guideline on Diagnosis and Treatment of Aortic Aneurysm and Aortic Dissection. *Circ J*. 2023 Sep 25;87(10):1410-1621. PMID: 37661428.
26. Committee for Scientific Affairs, The Japanese Association for Thoracic Surgery; Matsumiya G, Sato Y, Takeuchi H, Abe T, Endo S, Hirata Y, Ishida M, Iwata H, Kamei T, Kawaharada N, Kawamoto S, Kohno K, Kumamaru H, Minatoya K, Motomura N, Nakahara R, Okada M, Saji H, Saito A, Shimizu H, Suzuki K, Takemura H, Taketani T, Toh Y, Tatsuishi W, Yamamoto H, Yasuda T, Watanabe M, Yoshimura N, Tsuchida M, Sawa Y. Thoracic and cardiovascular surgeries in Japan during 2020 : Annual report by the Japanese Association for Thoracic Surgery. *Gen Thorac Cardiovasc Surg*. 2024 Jan;72(1):61-94.
 27. Chida-Nagai A, Masaki N, Maeda K, Sasaki K, Sato H, Muneuchi J, Ochiai Y, Murayama H, Tahara M, Shiono A, Shinozuka A, Kono F, Machida D, Toyooka S, Sugimoto S, Nakamura K, Akagi S, Kondo M, Kasahara S, Kotani Y, Koizumi J, Oda K, Harada M, Nakajima D, Murata A, Nagata H, Yatsunami K, Kobayashi T, Matsunaga Y, Inoue T, Yamagishi H, Nakagawa N, Ohtani K, Yamamoto M, Ito Y, Hokosaki T, Kuwahara Y, Masutani S, Nomura K, Wada T, Sawada H, Abiko M, Takahashi T, Ishikawa Y, Okada S, Naitoh A, Toda T, Ando T, Masuzawa A, Hoshino S, Kawada M, Nomura Y, Ueno K, Ohashi N, Tachibana T, Cao Y, Ueda H, Yanagi S, Koide M, Mitsushita N, Higashi K, Minosaki Y, Hayashi T, Okamoto T, Kuraishi K, Ehara E, Ishida H, Horigome H, Murakami T, Takei K, Ishii T, Harada G, Hirata Y, Maeda J, Tatebe S, Ota C, Hayabuchi Y, Sakazaki H, Sasaki T, Hirono K, Suzuki S, Yasuda M, Takeda A, Sawai M, Miyaji K, Kitagawa A, Nakai Y, Kakimoto N, Agematsu K, Manabe A, Saiki Y. Use of the index of pulmonary vascular disease for predicting long-term outcome of pulmonary arterial hypertension associated with congenital heart disease. *Front Cardiovasc Med*. 2023 Sep 4;10:1212882. PMID: 37731527.
 28. Committee for Scientific Affairs, The Japanese Association for Thoracic Surgery; Minatoya K, Sato Y, Toh Y, Abe T, Endo S, Hirata Y, Ishida M, Iwata H, Kamei T, Kawaharada N, Kawamoto S, Kohno K, Kumamaru H, Matsumiya G, Motomura N, Nakahara R, Okada M, Saji H, Saito A, Shimizu H, Suzuki K, Takemura H, Taketani T, Takeuchi H, Tatsuishi W, Yamamoto H, Yasuda T, Watanabe M, Yoshimura N, Tsuchida M, Sawa Y. Thoracic and cardiovascular surgeries in Japan during 2019: Annual report by the Japanese Association for Thoracic Surgery. *Gen Thorac Cardiovasc Surg*. 2023 Oct;71(10):595-628.
 29. Ishii S, Fujiwara T, Yagi H, Takeda N, Ando M, Yamauchi H, Inuzuka R, Taniguchi Y, Hatano M, Komuro I. A novel pathogenic variant located just upstream of the C-terminal Ser423-X-Ser425 phosphorylation motif in SMAD3 causing Loeys-Dietz syndrome. *Mol Genet Genomic Med*. 2023 Dec;11(12):e2257. PMID: 37864304.

Department of Gastrointestinal Surgery

Professor

Yasuyuki Seto M.D. Ph.D.

Associate Professor

Sachiyo Nomura M.D. Ph.D.

Susumu Aikou M.D. Ph.D.(The Institute of Medical Science)

Lecturer

Koichi Yagi M.D. Ph.D.

Associates

Shoh Yajima M.D. Ph.D.

Kei Sakamoto MD, PhD

Yoshiyuki Miwa M.D. Ph.D

Masayuki Urabe M.D. Ph.D.

Shuichiro Oya M.D. Ph.D

Asami Okamoto M.D. Ph.D.

Homepage <https://plaza.umin.ac.jp/~todai3ge/>

General Affairs:

Since 1997, the former Third Department of Surgery, which was located in a branch hospital of the University of Tokyo, has been divided into two departments, the Department of Gastrointestinal Surgery and the Department of Metabolic Care and Endocrine Surgery, in line with the integration of the main and branch hospitals. Department of Metabolic Care and Endocrine Surgery has been renamed Breast and Endocrine Surgery in April 2017.

With the prolongation of life expectancy, there are increasing numbers of multi-morbid patients requiring multi-organ treatment, as well as a greater need for multidisciplinary approaches to the patients. Our fundamental principles of patient treatment are comprehensive patient care which includes pre-, peri-, and postoperative management of the diseases as well as patient care over long-term postoperative periods which often extend to the terminal stage. We believe that patient care encompassing the entire lifespan

provides a wealth of valuable information concerning the appropriateness of current treatment strategy, the establishment of new surgical designs, the development of new basic research activities which can much contribute to clinical fields, and indications of desirable modes of terminal care.

Fostering good surgeons as well as scientists who meet both clinical and academic needs has always been the guiding principle of our department.

Educational Activities:

The new system of clinical clerkship for medical students has begun from 2013. During those periods, the students are educated strictly and gently by staffs. Clinical exercises, e.g., blood sampling, injection, and ligation, laparoscopic training, etc., are performed. They can attend the operations as an assistant.

They learn general patient care which encompasses not only perioperative management of diseases but also non-surgical management of postoperative

disorders and terminal care. Our educational system provides medical students with a great deal of practical information from the medical point of view as well as better opportunities to ponder the implications of life and death.

For the medical students, the clinical clerkship lectures are held two times a week. The experts (from outside hospital) other than the staff give special unique and informative lectures, which are popular among the students.

Intern doctors rotate every three or one and half months. After completion of their initial training program, they go into a further exclusive clinical training program for several consecutive years and become a chief resident.

Research Activities:

Our goal is to cure the cancer patients by much better surgery. The development of better surgical methods has the highest priority. Better surgery means radicality of the cancer control, minimal invasiveness, and good QOL after surgery. Recently, transmediastinal (non-transthoracic) radical esophagectomy with extended lymphadenectomy has been applied, which shows less pulmonary complications, shorter postoperative hospital stay and better QOL after surgery. To develop this surgical procedure, we and other surgeons sharing same will established the Japanese Society for Nontransthoracic Radical Esophagectomy in 2016. New methods of endoscopic/laparoscopic full-thickness resection, non-exposed endoscopic wall-inversion surgery (NEWS) has been developed for submucosal gastric tumor as a collaboration of endoscopy and laparoscopy, and now NEWS is applied for some gastric cancer. Elimination of the pulmonary complications after esophagectomy and the detection of minute metastasis for the establishment of better surgery are also our important targets.

Another main research activities of the department of Gastrointestinal Surgery has been focused on diagnosis and therapy for gastrointestinal diseases and clinical and basic research for gastrointestinal carcinogenesis from the view point of "Surgery and Inflammation". The department's research activities have focused on a wide spectrum of research topics,

ranging from basic research topics to clinical ones. Our research activities have been well organized and ultimately achieved by maintaining a close connection between hospital and laboratory activities. Our medical staffs make every effort to promote the research activities and obtain successful results.

Clinical Activities:

We have outpatient clinics from Monday through Friday. We have specialized divisions for outpatient management of esophageal, gastric diseases. The ward is divided into two subgroups, and each of them has one medical staff for supervision, one assistant supervisor, one chief resident, and one or two junior residents in rotation. They are on duty for daily patient care under the supervision of medical staffs. Ordinary, each subgroup takes care of 15-25 patients.

The weekly official activities of our department are Ward Rounds by the Professor on Monday. We have post- and preoperative case conferences on Wednesday, and Thursday morning, respectively, and a journal club (online) on Monday. We also have a specialized upper gastrointestinal case conference on Thursday evening. Further, cancer board is held, where the endoscopists, head and neck surgeons, and radiologists as well as surgeons attend together and have discussions frankly.

Generally, elective surgery is scheduled on Tuesday, Wednesday and Thursday. The statistics shows 80 gastric and 50 esophageal cancer surgeries are performed a year, respectively. Hernia surgery is also performed. Laparoscopic sleeve gastrectomy for morbid obesity has started in June 2016, and the number of cases is steadily increasing. All residents and medical personnel work with high motivation for the good of the patients.

References

1. Takahashi K, Higashizono K, Fukatsu K, Murakoshi S, Takayama H, Noguchi M, Matsumoto N, Seto Y. Prehabilitation Ameliorates Gut Ischemia Reperfusion Injury in Mice. *J Surg Res* 282:71-83. doi: 10.1016/j.jss.2022.08.033,2023
2. Ri M, Narita T, Urabe M, Yoshimura S, Yajima S, Okumura Y, Yagi K, Seto Y. Effects of the

- preoperative use and dosage of steroids on postoperative complications of gastric cancer surgery. *Surg Today*; 53(10):1173-80. doi: 10.1007/s00595-023-02698-6 ,2023
3. Konishi T, Sasabuchi Y, Tanabe M, Seto Y, Yasunaga H. ASO Author Reflections: Age at Oncological Surgery Affects the Long-Term Risk of Being Bedridden in Elderly Patients. *Ann Surg Oncol* 30(8):4613-14. doi:10.1245/s10434-023-13583-4,2023
 4. Konishi T, Ono S, Okada A, Matsui H, Tanabe M, Seto Y, Yasunaga H. Erratum: Comparison of bleeding following gastrointestinal endoscopic biopsy in patients treated with and without direct oral anticoagulants. *Endosc Int Open* 11(1):C2. doi: 10.1055/a-2031-2897,2023
 5. Urabe M, Matsusaka K, Ushiku T, Fukuyo M, Rahmutulla B, Yamashita H, Seto Y, Fukayama M, Kaneda A. Adenocarcinoma of the stomach and esophagogastric junction with low DNA methylation show poor prognoses. *Gastric Cancer* 26(1):95-107. doi: 10.1007/s10120-022-01344-3,2023.
 6. Yamashita S, Abe H, Yamashita H, Yagi K, Seto Y, Ushiku T. PD-L1 and HLA- class I expression status and their therapeutic implication in oesophageal small-cell carcinoma. *Histopathology* 83(2):264-75. doi:10.1111/his.14924,2023
 7. Konishi T, Sasabuchi Y, Matsui H, Tanabe M, Seto Y, Yasunaga H. ASO Visual Abstract: Long-Term Risk of Being Bedridden in Elderly Patients Who Underwent Oncologic Surgery-A Retrospective Study Using a Japanese Claims Database. *Ann Surg Oncol* 30(8):4615-6. doi: 10.1245/s10434-023-13566-5,2023
 8. Mita H, Katoh H, Komura D, Kakiuchi M, Abe H, Rokutan H, Yagi K, Nomura S, Ushiku T, Seto Y, Ishikawa S. Aberrant Cadherin11 expression predicts distant metastasis of gastric cancer. *Pathol Res Pract* 242:154294. doi: 10.1016/j.prp.2022.154294, 2023
 9. Konishi T, Tanabe M, Michihata N, Matsui H, Nishioka K, Fushimi K, Seto Y, Yasunaga H. Risk factors for arm lymphedema following breast cancer surgery: a Japanese nationwide database study of 84,022 patients. *Breast Cancer* 30(1):36-45. doi: 10.1007/s12282-022- 01395-5, 2023
 10. Konishi T, Fujiogi M, Sato M, Michihata N, Matsui H, Nishioka K, Tanabe M, Seto Y, Yasunaga H. Impact of the National Action Plan for Antimicrobial Resistance on Antibiotic Use for Mastitis Using a Japanese Nationwide Database. *Breast Care (Basel)* 18(2):122-9. doi: 10.1159/000529381,2023
 11. Shiomi S, Yagi K, Iwata R, Yajima S, Okumura Y, Aikou S, Yamashita H, Nomura S, Seto Y. Lymphatic flow mapping using near-infrared fluorescence imaging with indocyanine green helps to predict lymph node metastasis intraoperatively in patients with esophageal or esophagogastric junction cancer not treated with neoadjuvant chemotherapy. *Surg Endosc* 37(11):8214-26. doi:10.1007/s00464-023-10368-4,2023
 12. Konishi T, Sasabuchi Y, Matsui H, Tanabe M, Seto Y, Yasunaga H. Long-Term Risk of Being Bedridden in Elderly Patients Who Underwent Oncologic Surgery: A Retrospective Study Using a Japanese Claims Database. *Ann Surg Oncol* 30(8):4604-12. doi: 10.1245/s10434- 023-13566-5,2023
 13. Otsuji K, Tanabe M, Morizono A, Harada M, Sato A, Niwa T, Nishioka K, Seto Y. Exploring Predictive Risk Factors of Infusion Reactions with First Pertuzumab Administration in HER2-positive Breast Cancer Patients: A Single Institution Experience. *JMA J* ;6(1):63-72. doi: 10.31662/jmaj.2022-0132,2023
 14. Mita H, Katoh H, Komura D, Kakiuchi M, Abe H, Rokutan H, Yagi K, Nomura S, Ushiku T, Seto Y, Ishikawa S. Aberrant Cadherin11 expression predicts distant metastasis of gastric cancer. *Pathol Res Pract* 242:154294. doi:10.1016/j.prp.2022.154294,2023
 15. Suzuki Y, Hanaoka S, Tanabe M, Yoshikawa T, Seto Y. Predicting Breast Cancer. Risk Using Radiomics Features of Mammography Images. *J Pers Med*;13(11):1528. doi: 10.3390/jpm13111528,2023
 16. Sato Y, Yamashita H, Kobayashi Y, Nagaoka K, Hisayoshi T, Kawahara T, Kuroda A, Saito N, Iwata R, Okumura Y, Yagi K, Aiko S, Nomura S,

- Kakimi K, Seto Y. Alterations in Intratumoral Immune Response before and during Early-On Nivolumab Treatment for Unresectable Advanced or Recurrent Gastric Cancer. *Int J Mol Sci* 24(23):16602. doi: 10.3390/ijms242316602,2023
17. Mitsui T, Saito K, Hakozaiki Y, Miwa Y, Noro T, Takeshita E, Urahashi T, Seto Y, Okuyama T, Yoshitomi H. Novel Clean End-to-End Anastomosis Method, Without Opening the Stomach Lumen, in Totally Laparoscopic or Robotic Pylorus-Preserving Gastrectomy. *J Gastric Cancer* 23(4):523-34. doi:10.5230/jgc.2023.23.e33,2023
 18. Urabe M, Okumura Y, Okamoto A, Yagi K, Tsuji Y, Yamashita H, Fujishiro M, Seto Y. Laparoscopic and endoscopic cooperative surgery as palliative treatment for elderly patients with gastric cancer. *Nagoya J Med Sci* 85(4):807-13. doi: 10.18999/nagjms.85.4.807,2023
 19. Urabe M, Yagi K, Yoshimura S, Ri M, Yajima S, Okumura Y, Seto Y. Duodenal diversion surgery in management of intractable tracheobroncho-gastric fistula after esophagectomy. *Gen Thorac Cardiovasc Surg Case* 2(1): 58,2023

Hepato-biliary-Pancreatic Surgery Division and Artificial Organ and Transplantation Division

Professor and Chairman

Kiyoshi Hasegawa, M.D., Ph.D.

Associate Professor

Nobuhisa Akamatsu, M.D., Ph.D.

Yoshikuni Kawaguchi, M.D., Ph.D.

Lecturers

Junichi Kaneko, M.D., Ph.D.

Akihiko Ichida, M.D., Ph.D.

Homepages <http://www.u-tokyo-hbp-transplant-surgery.jp/>

Introduction and Organization

The Hepato-Biliary-Pancreatic (HBP) Surgery Division, Artificial Organ and Liver Transplantation Division, Department of Surgery is originated from Second Department of Surgery (2nd Dept of Surg), which was established in 1893. This department has a history of over 130 years and has made tremendous contribution to the Japanese surgical advancement, such as the foundation of Japanese Surgical Society. As departments in the style of graduate school have been increasingly founded in The University of Tokyo, and organ-specific medication has been progressively recommended, 2nd Dept of Surg has been replaced to HBP Surg Division since June 1st, 1998.

Clinical Activities

Our division deals with patients with HBP malignancies, benign diseases and end stage liver disease. We specialize in hepatectomies for hepatocellular carcinoma and colorectal metastasis. Laparoscopic or robotic Whipple's procedure has started recent year. Living donor liver transplantation

achieved international renown. Now we are ranked in the top three high volume centers in Japan including deceased donor liver transplantation. Roughly 500 patients undergo surgery every year. Elective operations are carried out on Monday, Wednesday and Friday. The perioperative management is strictly controlled, with nearly zero mortality. Adjuvant chemotherapy is performed in a style of prospective clinical trials.

Education

Education for medical students includes systematic lectures of surgery for M2 (senior year) students, and clinical lectures and bed-side practice for M3 and final-year students, in accordance with other surgical and non-surgical departments. Since 2013, The Clinical Clerkship, more practical medical training had started. In our division, students actively participate the surgical activities.

Clinical Clerkship is designed to consist of 2 parts; 2 weeks clinical practice in the University of Tokyo and 1 week practice in other hospitals. Medical students are expected to join the surgical team and the

surgical operations. They can learn about preoperative examinations & care of the patients, informed consents, diagnosis, presentation at the conferences, operative procedures, and postoperative managements. They also are expected to submit a report on a theme of specific surgical topics.

Research

We have published papers mainly on HBP Surgery and liver transplantation. The ongoing topics involve clinical application of ICG fluorescence imaging enabling visualization of biological structures (biliary trees, hepatic tumors, hepatic segmental boundaries, etc.), prospective clinical trials of adjuvant chemotherapy for hepatocellular carcinoma, metastatic colorectal cancer, neoadjuvant chemotherapy for borderline resectable pancreatic cancer, utility of contrast-enhanced intraoperative ultrasonography, pre operative navigation for hepatic surgery, and clinical application of artificial intelligence and synthetic blood vessel graft.

Publications (2023)

1. Ito D, Kawaguchi Y, Inagaki Y, Ito K, Mihara Y, Kaneko J, Tanaka M, Fukayama M, Kokudo N, Hasegawa K. Assessment of liver function-related mRNA expression and fluorescence imaging in outflow-obstructed regions in rats. *Surg Today*. 2023 Apr;53(4):513-521.
2. Fukuda K, Kawaguchi Y, Abe S, Kobayashi Y, Maki H, Akamatsu N, Kaneko J, Arita J, Hasegawa K. Safety and usefulness of fluorescence imaging using methylene blue as a fluorophore in a Japanese population with hepatobiliary and pancreatic diseases: A phase I study. *J Hepatobiliary Pancreat Sci*. 2023 Jul;30(7):863-870.
3. Kokudo T, Kokudo N, Hasegawa K. Oncological benefit of anatomic resection for patients with hepatocellular carcinoma. *Surg Today*. 2023 Oct; 53(10):1216.
4. Ichida A, Kokudo T, Shimada S, Hatano E, Kubo S, Kato Y, Ishikawa Y, Mori A, Baba H, Matsuyama Y, Endo I, Yamaue H, Yamamoto M, Kokudo N, Hasegawa K. Liver Resection for Hepatocellular Carcinoma With Tumor Thrombus in the Inferior Vena Cava or Right Atrium: A Large-scale Multicenter Survey Conducted in Japan. *Ann Surg*. 2023 Sep 1;278(3):e549-e555.
5. Kiritani S, Iwano T, Yoshimura K, Saito R, Nakayama T, Yamamoto D, Hakoda H, Watanabe G, Akamatsu N, Arita J, Kaneko J, Takeda S, Ichikawa D, Hasegawa K. New Diagnostic Modality Combining Mass Spectrometry and Machine Learning for the Discrimination of Malignant Intraductal Papillary Mucinous Neoplasms. *Ann Surg Oncol*. 2023 May;30(5):3150-3157.
6. Yoshizaki Y, Kawaguchi Y, Seki Y, Sasaki S, Ichida A, Akamatsu N, Kaneko J, Arita J, Hasegawa K. Posthepatectomy but not prehepatectomy chemotherapy was associated with a longer time to recurrence in patients with resectable colorectal liver metastases: Inverse probability of treatment weighting analysis. *J Hepatobiliary Pancreat Sci*. 2023 Aug;30(8):1006-1014.
7. Hakoda H, Akamatsu N, Shibata E, Takao H, Ichida A, Kawaguchi Y, Kaneko J, Abe O, Hasegawa K. Interventional treatment for portal vein complications utilizing a hybrid operating room after liver transplantation. *HPB (Oxford)*. 2023 May;25(5): 589-592.
8. Karako K, Mihara Y, Hasegawa K, Chen Y. Improving the sensitivity of liver tumor classification in ultrasound images via a power-law shot noise model. *Biosci Trends*. 2023 May 15;17(2): 117-125.
9. Kaneko J, Ichida A, Kawaguchi Y, Hasegawa K. Pancreaticoduodenectomy: how to handle a replaced right hepatic artery. *Hepatobiliary Surg Nutr*. 2023 Apr 10;12(2):280-283.
10. Maki H, Kawaguchi Y, Nagata R, Mihara Y, Ichida A, Ishizawa T, Akamatsu N, Kaneko J, Arita J, Hasegawa K. Conditional recurrence analysis of intrahepatic cholangiocarcinoma: Changes in recurrence rate and survival after recurrence resection by disease-free interval. *Hepatol Res*. 2023 Dec;53(12):1224-1234.
11. Takao M, Kawaguchi Y, Matsumura M, Kazami Y, Tanimoto M, Abe S, Maki H, Ishizawa T, Arita J, Akamatsu N, Kaneko J, Kokudo N, Hasegawa K. Probe-based confocal laser endomicroscopy for real-time evaluation of colorectal liver metastasis in resected surgical specimens. *Hum Cell*. 2023 Nov; 36(6):2066-2073.

12. Kazami Y, Kaneko J, Keshwani D, Kitamura Y, Takahashi R, Mihara Y, Ichida A, Kawaguchi Y, Akamatsu N, Hasegawa K. Two-step artificial intelligence algorithm for liver segmentation automates anatomic virtual hepatectomy. *J Hepatobiliary Pancreat Sci*. 2023 Nov;30(11):1205-1217.
13. Takahashi R, Ishizawa T, Inagaki Y, Tanaka M, Ogasawara A, Kuriki Y, Fujita K, Kamiya M, Ushiku T, Urano Y, Hasegawa K. Real-Time Fluorescence Imaging to Identify Cholangiocarcinoma in the Extrahepatic Biliary Tree Using an Enzyme-Activatable Probe. *Liver Cancer*. 2023 Apr 14;12(6):590-602.
14. Watanabe G, Ishizawa T, Kuriki Y, Kamiya M, Ichida A, Kawaguchi Y, Akamatsu N, Kaneko J, Arita J, Kokudo N, Urano Y, Hasegawa K. Evaluation of pancreatic chymotrypsin activity for on-site prediction of clinically relevant postoperative pancreatic fistula. *Pancreatology*. 2024 Feb; 24(1):169-177.
15. Kawaguchi Y, Yoshizaki Y, Kawakami T, Iwamoto M, Hayakawa T, Hayashi Y, Sawa Y, Ito K, Kashiwabara K, Akamatsu N, Kaneko J, Nishikata Y, Hasegawa K. Effect of Smoke Evacuator on Reduction of Volatile Organic Compounds and Particles in Surgical Smoke: A Randomized Controlled Trial. *J Am Coll Surg*. 2024 Mar 1; 238(3):272-279.
16. Nagata R, Akamatsu N, Shibata E, Takao H, Ichida A, Mihara Y, Kawaguchi Y, Ishizawa T, Kaneko J, Arita J, Tamura S, Abe O, Hasegawa K. Metallic Stents for Hepatic Venous Outflow Obstruction After Living-Donor Liver Transplantation and their Therapeutic Effects. *Transplant Proc*. 2024 Jan-Feb; 56(1):125-134.
17. Abe S, Nakai Y, Arita J, Ichida A, Kawaguchi Y, Akamatsu N, Kaneko J, Ijichi H, Koike K, Fujishiro M, Hasegawa K. The Effect of Renin-Angiotensin System Inhibitors in Patients Undergoing Pancreatic Cancer Resection. *Pancreas*. 2024 Mar 1;53(3):e233-e239.
18. Fukuda K, Kaneko J, Kiritani S, Sawa Y, Morito M, Tanaka M, Ushiku T, Cheng CJ, Tanaka T, Tanaka R, Asakura T, Kawaguchi Y, Akamatsu N, Hasegawa K. Thick silk fibroin vascular graft: A promising tissue-engineered scaffold material for abdominal vein grafts in middle-sized mammals. *Int J Artif Organs*. 2024 Mar;47(3):190-197.
19. Kaneko J, Hayashi Y, Kazami Y, Nishioka Y, Miyata A, Ichida A, Kawaguchi Y, Akamatsu N, Hasegawa K. Resection and reconstruction of the largest abdominal vein system (the inferior vena cava, hepatic, and portal vein): a narrative review. *Transl Gastroenterol Hepatol*. 2024 Mar 21;9:23.
20. Ichida A, Arita J, Hatano E, Eguchi S, Saiura A, Nagano H, Shindoh J, Hashimoto M, Takemura N, Taura K, Sakamoto Y, Takahashi Y, Seyama Y, Sasaki Y, Uemura K, Kokudo N, Hasegawa K. A Multicenter Phase 2 Trial Evaluating the Efficacy and Safety of Preoperative Lenvatinib Therapy for Patients with Advanced Hepatocellular Carcinoma (LENS-HCC Trial). *Liver Cancer*. 2023 Nov 28; 13(3):322-334.

Department of Urology

Professor

Haruki Kume, M.D., Ph.D.

Assistant Professor

Daisuke Yamada, M.D., Ph.D. Yusuke Sato, M.D., Ph.D. Yuta Yamada, M.D., Ph.D.,
Yoshiyuki Akiyama, M.D., Ph.D. Satoru Taguchi, M.D., Ph.D. Jun Kamei, M.D., Ph.D.

Associate

Kenji Yoda, M.D., Kanae Yoshida, M.D., Mami Kato, M.D., Yoichi Fujii, M.D., Ph.D.,
Daiji Watanabe, M.D., Hideyuki Minagawa, M.D., Ibuki Tsuru, M.D.,
Ryo Tanaka, M.D., Kazuki Akiyama, M.D., Masato Kanou, M.D., Yusuke Kubota, M.D.,
Shinnosuke Oishi, M.D., Kenichi Hashimoto, Ph.D.

Homepage <http://www.h.u-tokyo.ac.jp/urology/>

Introduction and Organization

Urology is a special field of clinical medicine covering the diseases of the adrenal gland, the kidney, the urinary tract and the male genital system by means of a surgical procedure as well as an approach of internal medicine. In addition, urology encompasses pediatric urology, neurourology, female urology, renal transplantation, renal vascular surgery, endocrine surgery and geriatric urology. For this reason, urology requires the scientific background of oncology, nephrology, endocrinology, andrology, immunology, pediatrics, histology, microbiology, neurology and gerontology. Now we have commenced to utilize cellular and molecular biology to develop the research in urology. It is expected for our department to devote to the scientific progress in the frontier of urology.

In recent years, we have been taking international leadership in applying the new and minimally invasive treatment modalities. They are exemplified by endoscopic management of the diseases in the upper urinary tract, ESWL or laser lithotripsy for urolithiasis, hyperthermic and laser therapies for BPH, and minimum incision endoscopic or laparoscopic adrenalectomy, nephrectomy, and robot-assisted

prostatectomy substituting open procedures.

Clinical activities

There are 44 beds in the ward (8th floor of the central-ward-building). The professor, associate professors, lecturers and associates are involved in in-patient and out-patient cares and teaching of the students as well as research activities. Clinical visiting professors are mainly engaged in the teaching. The residents take care of all the patients on 24-hour a day basis. Associate staff members team up with the residents on a man-to-man basis. Elective operations are performed on every weekday (from Monday to Friday). 1,828 operations were performed in 2023. The numbers of main operations are adrenalectomy 11, nephrectomy 26, partial nephrectomy 44, nephroureterectomy 25, radical cystectomy 12, radical prostatectomy 155, transurethral resection of the bladder tumor (TURBT) 202, transurethral resection of the prostate (TURP) 5, and robot-assisted surgeries 212 (radical prostatectomy 155, partial nephrectomy 39, radical cystectomy 10, pyeloplasty 8).

At the weekly professor's round on Wednesday, data of all in patients are presented and appropriate

treatment strategies are recommended for them. On Wednesday evening, a clinical conference is held for discussing cases with difficult problems in detail and the best treatment is chosen for each case.

In out-patient clinic, services are provided from Monday to Friday. Patients assigned to specialized services as renal tumor, adrenal surgery, bladder cancer, prostate cancer, andrology, neurourology, urolithiasis, kidney transplantation, second opinion, pediatric urology and female urology receive sophisticated care on the particular day of the week.

The total number of out-patients was 26,512 patient-days from January 2023 to December 2023.

Teaching activities

Systematic urological lectures are provided for second year medical students. Both clinical lectures and bed side teaching are scheduled for third and fourth year medical students. Thirteen times of systematic lectures are performed by professor, associate professors and instructors concerning their specialties.

Bed side teaching is concentrated on practical care of the patients. Teachers give lectures mainly regarding pre- and post-operative management, indication of operation, surgical anatomy and surgical techniques.

Research activities

There are 9 research themes for research as below. The basic principles for research are program in surgical techniques and therapy for incurable diseases, which include advanced cancer, renal insufficiency, sexual dysfunction, and interstitial cystitis. We have published approximately 50 English papers every year.

Renal tumor

Urolithiasis

Kidney Transplantation

Prostate diseases

New surgical technique

Urinary disturbance/ Female Urology

Andrology

Virology

References

1. Nagamoto S, Urakami S, Oka S, Ogawa K, Kono K, Sakaguchi K, Kinowaki K, Yamada D, Kume H. Impact of the neutrophil-to-lymphocyte ratio as a surgical prognostic factor in renal cell carcinoma with inferior-vena-cava tumor thrombus. *Asian J Surg*, 46(1), 192-200, 2023.1.
2. Kaga K, Yamanishi T, Kamasako T, Kaga M, Fuse M, Ishizuka M. Efficacy of Transcutaneous Tibial Nerve Stimulaton with Silver Spike Point Electrodes for Refractory Overactive Bladder: A Single-Arm Study. *Cureus*, 15(1), e34166, 2023.1.
3. Tatenuma T, Ebara S, Kawase M, Sasaki T, Ikehata Y, Nakayama A, Toide M, Yoneda T, Sakaguchi K, Teishima J, Inoue T, Kitamura H, Saito K, Koga F, Urakami S, Koie T, Makiyama K. Association of hospital volume with perioperative and oncological outcomes of robot-assisted laparoscopic radical prostatectomy: a retrospective multicenter cohort study. *BMC Urol*, 23(1), 14, 2023.1.
4. Iwaki T, Akiyama Y, Nosato H, Kinjo M, Niimi A, Taguchi S, Yamada Y, Sato Y, Kawai T, Yamada D, Sakanashi H, Kume H, Homma Y, Fukuhara H. Deep Learning Models for Cystoscopic Recognition of Hunner Lesion in Interstitial Cystitis. *Eur Urol Open Sci*, 49, 44-50, 2023.1.
5. Nakamura M, Suzuki M, Izumi T, Tsuru I, Muraki Y, Kume H. Trends in surgical treatment for prostate cancer: Analysis of National Database Open Data in Japan. *Glob Health Med*, 5(1), 62-63, 2023.2.
6. Kurano M, Sumitani M, Akiyama Y, Yamada M, Fujimura D, Yamaki S, Kano K, Aoki J, Hayakawa K, Takahashi T, Hirai T, Okawa A, Kume H, Ogata T, Tanaka S, Chikuda H, Yatomi Y. Usefulness of lysophosphatidylcholine measurement in the cerebrospinal fluid for differential diagnosis of neuropathic pain: Possible introduction into clinical laboratory testing. *Clin Chim Acta*, 541, 117249, 2023.2.
7. Zhou J, Koizeumi N, Nishiyama Y, Kogiso K, Ishikawa T, Kobayashi K, Watanabe Y, Fujibayashi T, Yamada M, Matsuyama M, Tsukihara H, Tsumura R, Yoshinaka K,

- Matsumoto N, Ogawa M, Miyazaki H, Numata K, Nagaoka H, Iwai T, Iijima H. A VS ultrasound diagnostic system with kidney image evaluation functions. *Int J Comput Assist Radiol Surg*, 18(2), 227-246, 2023.2.
8. Ando S, Nakamura S, Hyuga T, Tanabe K, Nakai H, Fujimura T. Indigo Carmine Dye-Assisted Lymphatic-Sparing Microsurgical Subinguinal Varicocelelectomy Among Children and Adolescents. *Indian J Surg*, 85, 149-153, 2023.2.
9. Tohi Y, Ishikawa R, Kato T, Miyakawa J, Matsumoto R, Mori K, Mitsuzuka K, Inokuchi J, Matsumura M, Shiga K, Naito H, Kohjimoto Y, Kawamura N, Inoue M, Kinoshita H, Hashimoto K, Goto K, Haba R, Kakehi Y, Sugimoto M. Clinical outcomes of intraductal carcinoma or cribriform in radical prostatectomy specimens of men opting for active surveillance: data from the PRIAS-JAPAN study. *Int J Clin Oncol*, 28(2), 299-305, 2023.2.
10. Hakozaiki Y, Yamada Y, Takeshima Y, Taguchi S, Kawai T, Nakamura M, Iwaki T, Teshima T, Kinoshita Y, Akiyama Y, Sato Y, Yamada D, Suzuki M, Kume H. Low hemoglobin and PSA kinetics are prognostic factors of overall survival in metastatic castration-resistant prostate cancer patients. *Sci Rep*, 13(1), 2672, 2023.2.
11. Yamada Y, Nakagawa T, Miyakawa J, Kawai T, Taguchi S, Tabata M, Kaneko T, Ishikawa A, Miyazaki H, Kondo Y, Matsumoto A, Naito A, Hikatsu M, Fujii Y, Akiyama Y, Yamada Y, Sato Y, Nomiya A, Yamada D, Murata T, Suzuki M, Enomoto Y, Nishimatsu H, Takeuchi T, Tanaka Y, Kume H. Subclassification of pT3 upper tract urothelial carcinoma: A multicenter retrospective study. *World J Urol*, 41(3), 767-776, 2023.3.
12. Fukuhara h, Tsurumaki Sato Y, Hou J, Iwai M, Todo T. Fusion peptide is superior to co-expressing subunits for arming oncolytic herpes virus with interleukin 12. *Commun Med (Lond)*, 3(1), 40, 2023.3.
13. Kurokawa I, Nomura Y, Nakagawa C, Okada Y, Fuji K, Yoshimura Y. Transvaginal vesicovaginal fistula closure: A retrospective study of 28 cases at a single facility in Japan. *Int. J. Urol*, 30(7), 586-591, 2023.3.
14. Yamazaki M, Takayama T, Fujita A, Kikuchi T, Kamimura T, Myoga H, Mayumi S, Yazaki K, Katano S, Komatsubara M, Kamei J, Sugihara T, Ando S, Fujimura T. 3D printed kidney model could be an important educational tool for residents. *Asian J Endosc Surg*, 16(2), 197-202, 2023.4.
15. Kinjo M, Masuda K, Nakamura Y, Taguchi S, Tambo M, Fukuhara H. Does metabolic syndrome influence the efficacy of mirabegron treatment in female patients with overactive bladder?. *Int Urogynecol J*, 34(4), 853-859, 2023.4.
16. Sasaki T, Ebara S, Tatenuma T, Ikehata Y, Nakayama A, Kawase M, Toide M, Yoneda T, Sakaguchi K, Teishima J, Makiyama K, Kitamura H, Saito K, Koie T, Koga F, Urakami S, Inoue T. Prognostic differences among the positive surgical margin locations following robot-assisted radical prostatectomy in a large Japanese cohort(the MSUG94 group). *Jpn J Clin Oncol*, 53(5), 443-451, 2023.4.
17. Kinjo M, Masuda K, Nakamura Y, Miyakawa J, Tambo M, Fukuhara H. Comparison of mirabegron and vibegron in women with treatment-naive overactive bladder: a randomized controlled study. *Urology*, 175, 67-73, 2023.5.
18. Kamei J, Sugihara T, Yasunaga H, Matsui H, Sasabuchi Y, Fujimura T, Homma Y, Kume H. Impact of early ureteral drainage on mortality in obstructive pyelonephritis with urolithiasis: an analysis of the Japanese National Database. *World J Urol*, 41(5), 1365-1371, 2023.5.
19. Ochiai K, Mochida Y, Nagase T, Fukuhara H, Ymaguchi Y, Nagase M. Upregulation of piezo2 in the mesangial, renin, and perivascular mesenchymal cells of the kidney of Dahl salt-sensitive hypertensive rats and its reversal by esaxerenone. *Hypertens Res*, 46(5), 1234-1246, 2023.5.
20. Kaneko T, Yanagida K, Matsui K, Yoshida T, Kawai T, Yamada Y, Ishii K, Kurozumi T, Suzuki T, Watanabe Y, Kawano H, Sakamoto T, Nakagawa T. Predictive factors of lower urinary tract injuries and spontaneous voiding failure after pelvic fractures. *In Vivo*, 37(3), 1323-1327, 2023.5.

21. Kaneko T, Yanagida K, Matsui K, Kawai T, Yamada Y, Ishii K, Kurozumi T, Suzuki T, Watanabe Y, Kawano H, Sakamoto T, Nakagawa T. Predictive Factors of Lower Urinary Tract Injuries and Spontaneous Voiding Failure After Pelvic Fractures. *In Vivo*, 37(3), 1323-1327, 2023.5.
22. Tabata M, Sato Y, Kogure Y, Marni B. McClure, Oshikawa-Kumade Y, Saito Y, Shingaki S, Ito Y, Yuasa M, Koya J, Yoshida K, Kohno T, Miyama Y, Morikawa T, Chiba K, Okada A, Ogawa S, Ushiku T, Shiraishi Y, Kume H, Kataoka K. Inter- and intra-tumor heterogeneity of genetic and immune profiles in inherited renal cell carcinoma. *Cell Rep*, 42(7), 112736, 2023.7.
23. Akiyama Y, Sonehara K, Maeda D, Katoh H, Naito T, Yamamoto K, Biobank Japan Project, Morisaki T, Ishikawa S, Ushiku T, Kume H, Homma Y, Okada Y. Genome-wide association analysis identifies susceptibility loci within the major histocompatibility complex region for Hunner-type interstitial cystitis. *Cell Rep Med*, 4(7), 101114, 2023.7.
24. Akiyama Y, Sonehara K, Maeda D, Katoh H, Naito T, Yamamoto K; Biobank Japan Project; Morisaki T, Ishikawa S, Ushiku T, Kume H, Homma Y, Okada Y. Genome-wide association study identifies risk loci within the major histocompatibility complex region for Hunner-type interstitial cystitis. *Cell Rep Med*, 4(7), 101114, 2023.7.
25. Tokura Y, Kawai T, Takei K, Ujiie T, Kanatani A, Yamada Y, Kaneko T, Kamai T, Nakagawa T. Geriatric 8 and Vulnerable Elders Survey-13 predict length of hospital stay and postoperative complications in Japanese patients undergoing urological surgery. *J Geriatr Oncol*, 14(6), 101558, 2023.7.
26. Miura Y, Motoshima T, Anami T, Yano H, Mito R, Pan C, Urakami S, Kinowaki K, Tsukamoto H, Kurahashi R, Murakami Y, Yatsuda J, Fujiwara Y, Kamba T, Komohara Y. Predictive value of CXCL10 for the occurrence of immune-related adverse events in patient with renal cell carcinoma. *Microbiol Immunol*, 67(7), 345-354, 2023.7.
27. Tokura Y, Kawai T, Takei K, Ujiie T, Kanatani A, Yamada Y, Kaneko T, Kamai T, Nakagawa T. Geriatric 8 and Vulnerable Elders Survey-13 predict length of hospital stay and postoperative complications in Japanese patients undergoing urological surgery. *J Geriatr Oncol*, 14(6), 101558, 2023.7.
28. Takahashi S, Takada I, Hashimoto K, Nakagawa T, Makishima M, Kume H. ESS2 controls prostate cancer progression through recruitment of chromodomain helicase DNA binding protein 1. *Sci Rep*. 13(1), 12355, 2023.7.
29. Kawase M, Ebara S, Tatenuma T, Sasaki T, Ikehata Y, Nakayama A, Toide M, Yoneda T, Sakaguchi K, Teishima J, Makiyama K, Inoue T, Kitamura H, Saito K, Koga F, Urakami S, Koie T. Clinical factors associated with biochemical recurrence of prostate cancer with seminal vesicle invasion followed by robot-assisted radical prostatectomy: a retrospective multicenter cohort study in Japan (the MSUG94 group). *J Robot Surg*, 17(4), 1609-1617, 2023.8.
30. Akiyama Y, Niimi A, Nomiya A, Taguchi S, Yamada Y, Sato Y, Yamada D, Maeda D, Ushiku T, Kume H, Homma Y. Efficacy and safety of low-dose oral prednisolone for patients with refractory Hunner-type interstitial cystitis. *Eur Urol Open Sci*, 56, 1-8, 2023.8.
31. Okuno Y, Hori M, Hattori-Kato M, Fukuhara H, Nomiya A, Mikami K, Takeuchi T. Structural Analysis of the Colony-Stimulating Factor 3 Gene of Granulocyte Colony-Stimulating Factor-Producing Urothelial Cancer. *Cureus*, 15(8), e43981, 2023.8.
32. Taguchi S, Kawai T, Buti S, Bersanelli M, Uemura Y, Kishitani K, Miyakawa J, Sugimoto K, Nakamura Y, Niimi F, Kaneko T, Kamei J, Obinata D, Yamaguchi K, Kakutani S, Kanazawa K, Sugihara Y, Tokunaga M, Akiyama Y, Yamada Y, Sato Y, Yamada D, Enomoto Y, Nishimatsu H, Fujimura T, Fukuhara H, Nakagawa T, Takahashi S, Kume H. Validation of a drug-based score in advanced urothelial carcinoma treated with pembrolizumab. *Immunotherapy*, 15(11), 827-837, 2023.8.
33. Nakamura M, Tsuru I (Co-first author), Izumi T, Ono A, Inoue Y, Muraki Y, Yamada Y, Tsuji Y,

- Watanabe J, Fujimura M, Kihara S, Naito A, Shiratori S, Amakawa R, Inatsu H, Yoshimatsu T, Kashiwagi M, Fukuda A, Morikawa T, Kusakabe M, Suzuki M, Kameyama S, Kume H, Shiga Y. Advantages of enhanced recovery after surgery program in robot-assisted radical cystectomy. *Sci Rep, Sci Rep*, 16237, 2023.9.
34. Hayashida M, Sakaguchi K, Yasuoka S, Tanaka M, Oshina T, Oka S, Tatsushima K, Takeshita A, Takeuchi Y, Urakami S. Perirenal fat thickness is a powerful predictor for surgical outcomes of transperitoneal laparoscopic adrenalectomy. *Int J Urol*, 31(1), 56-63, 2023.9.
 35. Okada y, Nakagawa C, Shigeta M, Nomura Y, Inoue E, Ichizuka K, Yoshimura Y. Evaluation of levator ani muscle elasticity after vaginal delivery and cesarean section using shear wave elastography. *J Med Ultrason* (2001), 51(1), 95-101, 2023.9.
 36. Nakamura M, Muraki Y, Tsuji Y, Watanabe J, Okabe K, Yamada Y, Kashiwagi M, Izumi T, Tsuru I, Fukuda A, Hayashi M, Matsumoto S, Kameyama S, Kume H, Shiga Y. Early experience with implementing Enhanced Recovery After Surgery protocol during robot-assisted radical prostatectomy. *AME Surgical Journal*, 2023.10.
 37. Hattori-Kato M, Okuno Y, Zaito M, Fukuhara H, Nomiya A, Mikami K, Takeuchi T. Hypomethylation of a CpG Site in the CpG Island of the Aquaporin 1 Gene May Be Involved in the Formation of Adult-Onset Non-communicating Hydrocele Testis. *Cureus*, 15(10), e47651, 2023.10.
 38. Tohi Y, Ishikawa R, Kato T, Miyakawa J, Matsumoto R, Mori K, Mitsuzuka K, Inokuchi J, Matsumura M, Shiga K, Naito H, Kohjimoto Y, Kawamura N, Inoue M, Akamatsu S, Terada N, Miyazawa Y, Narita S, Haba R, Sugimoto M. Increasing age predicts adverse pathology including intraductal carcinoma of the prostate and cribriform patterns in deferred radical prostatectomy after upfront active surveillance for Gleason grade group 1 prostate cancer: analysis of prospective observational study cohort. *Jpn J Clin Oncol*, 53(10), 984-990, 2023.10.
 39. Takeshima Y, Yamada Y, Takemura K, Kimura N, Hakozaiki Y, Miyakawa J, Taguchi S, Akiyama Y, Sato Y, Kawai T, Yamada D, Fujimura T, Kume H. The association between the parameters of uroflowmetry and lower urinary tract symptoms in prostate cancer patients after robot-assisted radical prostatectomy. *PLoS One*, 17(10), e0275069, 2023.10.
 40. Akiyama Y, Harada K, Miyakawa J, Karl J Kreder, Michael A O'Donnell, Maeda Daichi, Katoh H, Hori M, Owari K, Futami K, Ishikawa S, Ushiku T, Kume H, Homma Y, Yi Luo. Th1/17 polarization and potential treatment by an anti-interferon- γ DNA aptamer in Hunner-type interstitial cystitis. *iScience*, 26(11), 108262, 2023.10.
 41. Kawase M, Goto T, Ebara S, Tatenuma T, Sasaki T, Ishihara T, Ikehata Y, Nakayama A, Toide M, Yoneda T, Sakaguchi K, Teishima J, Kobayashi T, Makiyama K, Inoue T, Kitamura H, Saito K, Koga F, Urakami S, Koie T. Nomogram Predicting Locally Advanced Prostate Cancer in Patients with Clinically Organ-Confined Disease Who Underwent Robot-Assisted Radical Prostatectomy: A Retrospective Multicenter Cohort Study in Japan(The MSUG94 Group). *Ann Surg Oncol*, 30(11), 6925-6933, 2023.10.
 42. Oka S, Urakami S, Hagiwara K, Hayashida M, Sakaguchi K, Miura Y, Inoshita N, Arai M. The prevalence of lynch syndrome (DNA mismatch repair protein deficiency) in patients with primary localized prostate cancer using immunohistochemistry screening. *Hered Cancer Clin Pract*, 21(1), 20, 2023.10.
 43. Akiyama Y, Niimi A, Nomiya A, Taguchi S, Yamada Y, Sato Y, Kawai T, Yamada D, Kume H, Homma Y. Efficacy and safety of intravesical dimethyl sulfoxide treatment for patients with refractory Hunner-type interstitial cystitis: Real-world data postofficial approval in Japan. *Int J Urol*, Online ahead of print, 2023.10.
 44. Taguchi S, Onozawa M, Hinotsu S, Kawai T, Mitomi T, Uno S, Kume H. A multicenter, retrospective observational study investigating baseline characteristics and clinical outcomes in patients with hormone-sensitive prostate cancer treated with primary androgen deprivation

- therapy. *Jpn J Clin Oncol*, 53(10), 957-965, 2023. 10.
45. Oshima M, Takayama K, Yamada Y, Kimura N, Kume H, Fujimura T, Inoue S. Identification of DNA damage response-related genes as biomarkers for castration-resistant prostate cancer. *Sci Rep*, 13(1), 19602, 2023.11.
 46. Matsushima H. Validation of JSBMR's CTIBL manual for Japanese men receiving androgen deprivation therapy for prostate cancer. *J Bone Miner Metab*, 41(6), 822-828, 2023.11.
 47. Sakaguchi K, Ebara S, Tatenuma T, Sasaki T, Ikehata Y, Nakayama A, Kawase M, Toide M, Yoneda T, Teishima J, Makiyama K, Inoue T, Kitamura H, Saito K, Koie T, Koga F, Urakami S. Early and late urinary continence outcomes after unilateral and bilateral nerve-sparing robot-assisted radical prostatectomy: A retrospective multicentre cohort study in Japan (the MSUG94 group). *Int J Med Robot*, Online ahead of print, 2023.11.
 48. Taguchi S, Sugawara K, Gonoi W, Hanaoka S, Shiomi S, Kishitani K, Uemura Y, Akamatsu N, Inui S, Tanaka K, Yagi K, Kawai T, Nakagawa T, Fukuhara H, Abe O, Seto Y, Gonzalez MC, Prado CM, Kume H. The importance of ethnic-specific cut-offs of low muscle mass for survival prediction in oncology. *Clin Nutr*, 43(1), 134-141, 2023.11.
 49. Kimura T, Ishikawa H, Nagumo Y, Sekino Y, Kageyama Y, Ushijima H, Kawai T, Yamashita H, Azuma H, Nihei K, Takemura M, Hashimoto K, Maruo K, Tsuzuki T, Nishiyama H; BPT-ART Investigators Group. Efficacy and Safety of Bladder Preservation Therapy in Combination with Atezolizumab and Radiation Therapy (BPT-ART) for Invasive Bladder Cancer: Interim Analysis from a Multicenter, Open-label, Prospective Phase 2 Trial. *Int J Radiat Oncol Biol Phys*, 117(3), 644-651, 2023.11.
 50. Kawai T, Taguchi S, Nozaki K, Kimura N, Oshima T, Iwaki T, Matsui H, Niimi A, Kamei J, Akiyama Y, Yamada Y, Sato Y, Yamada D, Kaneko T, Sawayanagi S, Nakayama H, Minamimoto R, Yamashita H, Miyazaki H, Fujimura T, Nakagawa T, Kume H. Prostate-specific antigen doubling time predicts the efficacy of site-directed therapy for oligoprogressive castration-resistant prostate cancer. *Prostate Int*, 11(4), 239-246, 2023.12.
 51. Yamazaki M, Watanabe Y, Kawakami M, Takayama T, Furukawa H, Fujimura T. A new training model using the self-healing properties of supramolecular hydrogels for endoscopic combined intrarenal surgery. *Urolithiasis*, 52, 13, 2023.12.
 52. Ando S, Sugihara T, Hinotsu S, Kishino H, Hirata D, Watanabe R, Yanase A, Yokoyama H, Hoshina H, Endo K, Kamei J, Takaoka E, Fujimura T. Early recovery of urinary continence after robot-assisted radical prostatectomy is associated with membranous urethra and neurovascular bundle preservation. *Int J Urol*, Online ahead of print, 2023.12.
 53. Shiratori T, Nakamura M, Naito A, Yamamoto M, Ohkura Y, Yamakawa J, Kume H, Suzuki M. Clinical features and treatment outcomes of Fournier's gangrene in a single tertiary emergency hospital: Simplified Fournier's Gangrene Severity Index score is a predictor for death. *Glob Health Med*, 5(6), 362-365, 2023.12.
 54. Taguchi S, Kawai T, Ambe Y, Kishitani K, Sugimoto K, Miyakawa J, Nakamura Y, Noda M, Kaneko T, Kamei J, Obinata D, Yamaguchi K, Kakutani S, Furuya Y, Sato Y, Uemura Y, Akiyama Y, Yamada Y, Sato Y, Yamada D, Enomoto Y, Nishimatsu H, Fujimura T, Fukuhara H, Nakagawa T, Takahashi S, Kume H. Enfortumab vedotin versus platinum rechallenge in post-platinum, post-pembrolizumab advanced urothelial carcinoma: A multicenter propensity score-matched study. *Int J Urol*, 30(12), 1180-1186, 2023.12.
 55. Murase K, Kawase M, Ebara S, Tatenuma T, Sasaki T, Ikehata Y, Nakayama A, Toide M, Yoneda T, Sakaguchi K, Teishima J, Makiyama K, Inoue T, Kitamura H, Saito K, Koga F, Urakami S, Koie T. The Negative Impact of Inflammation-Related Parameters in Prostate Cancer after Robot-Assisted Radical Prostatectomy: A Retrospective Multicenter Cohort Study in Japan (the MSUG94 Group). *J Clin Med*, 12(24), 2023.12.

-
56. Fujiyama N, Tasaki M, Harata H, Tsutahara K, Matsumoto A, Kamijo Y, Toyoda M, Iwami D, Inui M, Shirakawa H, Sugimura J, Saito M, Okumi M, Saito K, Watarai Y, Hidaka Y, Ohtani K, Inoue N, Wakamiya N, Satoh S; Japanese Post-kidney Transplant TMA Support Team. Complement genetic backgrounds and clinical characteristics of patients with thrombotic microangiopathy within one week of kidney transplantation: A retrospective multicenter cross-sectional study in Japan. *Clin Exp Nephrol*, 27, 1010-1020, 2023.
 57. Noda M, Taguchi S, Shiraishi K, Fujimura T, Naito A, Kawai T, Kamei J, Akiyama Y, Yamada Y, Sato Y, Yamada D, Nakagawa T, Yamashita H, Nakagawa K, Abe O, Fukuhara H, Kume H. Six-year outcomes of robot-assisted radical prostatectomy versus volumetric modulated arc therapy for localized prostate cancer: A propensity score-matched analysis. *Strahlenther Onkol*, Online ahead of print, 2023.
 58. Yoshida T, Kawai T, Hagiwara K, Yanagida K, Noda M, Tokura Y, Yoshimura I, Kaneko T, Nakagawa T. Lower pretreatment serum testosterone level predicts poor prognosis in the patients with metastatic hormone-sensitive prostate cancer undergoing androgen deprivation therapy. *Jpn J Clin Oncol*, Online ahead of print, 2023.
 59. Kamei J, Endo K, Yamazaki M, Sugihara T, Takaoka EI, Ando S, Kume H, Fujimura T. Lower bleeding volume contributes to decreasing surgical site infection in radical cystectomy: A propensity score-matched comparison of open versus robot-assisted radical cystectomy. *Int J Urol*, Online ahead of print, 2023.

Department of Surgical Oncology

Professor

Soichiro Ishihara, M.D., Ph.D.

Associate Professor

Hiroaki Nozawa, M.D., Ph.D.

Lecturer

Kazuhito Sasaki, M.D., Ph.D., Koji Muroto, M.D., Ph.D.

Assistant Professor

Shigenobu Emoto, M.D., Ph.D., Hiroyuki Matsuzaki, M.D., Ph.D.,

Yuichiro Yokoyama, M.D., Ph.D., Shinya Abe, M.D., Ph.D., Yuzo Nagai, M.D., Ph.D.,

Takahide Shinagawa, M.D., Ph.D., Hirofumi Sonoda, M.D., Pharm.D., Ph.D.

Homepage <http://all-1su.umin.jp/>

Introduction and Organization

In 1995, a new system for postgraduate education was introduced. The First Department of Surgery was reorganized to form the Department of Surgical Oncology and the Department of Vascular Surgery. The staff of the Department of Surgical Oncology consists of one Professor, one Associate Professor, two Lecturers and seven Assistant Professors. The outpatient office is located on the third floor of the Outpatient Building. The ward is situated on the eighth floor of the Ward Building. The administrative office and research laboratories are located in the Administration and Research Building. Current activities of the Department of Surgical Oncology in clinical practice, education, and research are summarized as follows.

Clinical activities

The Department of Surgical Oncology provides comprehensive evaluation, diagnosis, treatment and management for adult patients with both general and oncologic surgical problems, in the ambulatory as well as inpatient setting. In particular, we are trying to identify the best way to treat each patient with the

least surgical stress by minimally invasive surgery such as laparoscopic surgery and robotic surgery (Da Vinci Surgical System, hinotori Surgical Robot System), and preoperative chemoradiotherapy, total neoadjuvant therapy for rectal cancer. The department is also well known for its innovative therapy for inflammatory bowel disease. Department specialists have expertise in biological cancer immunotherapy, chemotherapy for a variety of malignancies, and radiotherapy for rectal cancer. The outpatient clinic is open from Monday through Friday, and twenty-four-hour consultation is available for urgent or emergency problems.

The outpatient clinic is specialized in the lower GI tract. The Department was responsible for 493 surgically treated inpatients in the year of 2023. On Monday, Wednesday and Friday mornings, pre- and post-surgery conferences are held, and the Director's Round takes place after the conference every Wednesday. Operating days are Monday, Tuesday and Thursday. In addition to the clinical conferences, research conferences are held every Monday morning. Each research unit holds its own conference every week. Over 1200 colonoscopies are performed for a year. The newest technologies are introduced for

diagnosis and treatment of colon and rectal cancer and long-term surveillances for inflammatory bowel disease are performed.

Teaching activities

The Department of Surgical Oncology also offers a fellowship in surgical oncology for well-qualified surgeons who have completed their training in general surgery and wish to further specialize in surgical oncology. The Department of Surgical Oncology has a Surgical Oncology Training Program and provides broad reaching experience in technical aspects of diagnosis, treatment and management for adult patients with both surgical and oncologic problems, development of surgical judgment, and increasing knowledge about routine and complex conditions. In addition, the dedicated staff allows multiple opportunities for academic development both along clinical and basic scientific lines.

In the undergraduate education program, our department plays a role in the systemic lecture and in the clinical introduction lecture for the 2nd year medical students. We offer the clinical lectures and the bedside learning program for 3rd year medical students, in cooperation with other departments of surgery. In the systemic lectures on surgery, various fields were covered such as surgical oncology and immunology, injury, somatic reaction to surgery, infectious diseases, shock, pre- and post-surgical management and nutrition. In the clinical lectures, we presented many diseases such as colon cancer, colonic polyp, colonic polyposis and inflammatory bowel disease. In the postgraduate education program, new residents are trained to become qualified surgeons. In addition to pre- and post-surgery clinical conferences, the residents are expected to attend research conferences and seminars, which are held periodically. They are also asked to present cases at clinical meetings, which are held locally such as the local meeting of the Japanese Society of Gastroenterology.

Research activities

We apply the techniques used in molecular and cellular biology to our research. The following are the major themes under research.

1) Preoperative radiotherapy in lower rectal cancer

- 2) Cancer surveillance in ulcerative colitis
- 3) Carcinogenesis in ulcerative colitis
- 4) Laparoscopically assisted colon surgery
- 5) Local immunity in colorectal cancer
- 6) Genetic analysis of colorectal cancer and adenoma
- 7) Prognostic factor of early colorectal cancer
- 8) Surveillance program following colectomy for colorectal cancer
- 9) Analysis of factors associated with conversion surgery in initially unresectable/metastatic colorectal cancer
- 10) Cancer Immunotherapy targeting to the tumor vessels
- 11) Autophagy in Oncology
- 12) Lipid metabolism in carcinogenesis and tumor progression
- 13) Pathological studies in obstructive colorectal cancer
- 14) Genetic analysis on sensitivity to chemotherapeutic agents
- 15) Hemostasis and fibrinolysis in Oncology
- 16) Intraabdominal chemotherapy for peritoneal metastasis of gastric cancer
- 17) Pharmacokinetics in intraperitoneal chemotherapy
- 18) Clinical trials of chemotherapeutic drugs in metastatic colorectal cancer (single- or multi-institutional)
- 19) Single nucleotide polymorphisms (SNPs) in inflammatory bowel disease
- 20) Anatomy of vessels feeding the colon and rectum
- 21) High Frequency Ultrasonography (HIFU) for solid cancer
- 22) Quantitative analysis of intraperitoneal cancer cells in peritonitis carcinomatosis
- 23) Immunomodulation in chemoradiotherapy for locally advanced rectal cancer
- 24) Robot assisted laparoscopic colorectal surgery
- 25) Postoperative defecation function, urinary function, and sexual function after rectal cancer surgery
- 26) Application of 3D images and 3D printers in colorectal surgery
- 27) Navigation surgery
- 28) AI endoscopic diagnosis
- 29) AI pathological diagnosis
- 30) Microbiome in colorectal cancer

References

1. Abe S, Kawai K, Nozawa H, Sasaki K, Murono K, Emoto S, et al. Preoperative chemoradiotherapy using tegafur/uracil, oral leucovorin, and irinotecan (TEGAFIRI) followed by oxaliplatin-based chemotherapy as total neoadjuvant therapy for locally advanced rectal cancer: the study protocol for a phase II trial. *BMC Cancer*. 2023; 23(1):450.
2. Abe S, Nozawa H, Sasaki K, Murono K, Emoto S, Yokoyama Y, et al. Sarcopenia is Associated With Oncological Prognosis and the Incidence of Secondary Cancer in Patients With Middle/Lower Rectal Cancer. *Clin Colorectal Cancer*. 2023; 22(1):143-52.
3. Emoto S, Kawai K, Nozawa H, Sasaki K, Murono K, Yokoyama Y, et al. Prediction of lymph node metastasis of well-differentiated rectal neuroendocrine tumours using multiple diagnostic modalities. *Colorectal Dis*. 2023; 25(7):1414-22.
4. Fukui R, Nozawa H, Sakamoto A, Sasaki K, Murono K, Emoto S, et al. Temporal changes in functional outcomes of stapled and hand-sewn ileal pouch-anal anastomosis for ulcerative colitis and familial adenomatous polyposis. *Colorectal Dis*. 2023;25(3):396-403.
5. Kikuchi R, Emoto S, Nozawa H, Sasaki K, Murono K, Abe S, et al. Jejunal intussusception and perforation due to enteric muco-submucosal elongated polyp: a case report and literature review. *Surg Case Rep*. 2023;9(1):4.
6. Kikuchi R, Sasaki K, Nozawa H, Murono K, Emoto S, Yamauchi S, et al. Prognosis of Inferior Mesenteric and Para-aortic Lymph Node Metastases in Rectal Cancer: A Multicenter Study. *Anticancer Res*. 2023;43(9):4213-9.
7. Komatsu K, Nozawa H, Sonoda H, Abe S, Emoto S, Murono K, et al. Colectomy, especially right hemicolectomy, is a possible predisposing factor of omental torsion. *ANZ J Surg*. 2023;93(12):3006-7.
8. Lim S, Nagai Y, Nozawa H, Kawai K, Sasaki K, Murono K, et al. Surgical outcomes of robotic, laparoscopic, and open low anterior resection after preoperative chemoradiotherapy for patients with advanced lower rectal cancer. *Surg Today*. 2023;53(1):109-15.
9. Matsunaga K, Sasaki K, Hata K, Nozawa H, Kawai K, Murono K, et al. Clinical significance of the KRAS G13D mutation in anastomotic recurrence of colorectal cancer. *Oncol Lett*. 2023; 25(5):192.
10. Matsunaga K, Sasaki K, Nozawa H, Kawai K, Murono K, Yamauchi S, et al. Prognostic Significance of Enlarged Lymph Nodes in Stage II Colorectal Cancer. *Dis Colon Rectum*. 2023; 66(11):e1097-e106.
11. Murai S, Kawai K, Nozawa H, Sasaki K, Murono K, Emoto S, et al. Determination of the positional relationship of the second Houston valve and peritoneal reflection using computed tomographic colonography and magnetic resonance imaging. *Surg Today*. 2023;53(5):614-20.
12. Murono K, Yokoyama Y, Nozawa H, Sasaki K, Emoto S, Matsuzaki H, et al. Intraperitoneal paclitaxel combined with FOLFOX/CAPOX plus bevacizumab for colorectal cancer with peritoneal carcinomatosis (the iPac-02 trial): study protocol of a single arm, multicenter, phase 2 study. *Int J Colorectal Dis*. 2023;38(1):173.
13. Nagai Y, Kawai K, Nozawa H, Sasaki K, Murono K, Emoto S, et al. Three-dimensional visualization of the total mesorectal excision plane for dissection in rectal cancer surgery and its ability to predict surgical difficulty. *Sci Rep*. 2023;13(1):2130.
14. Noguchi T, Ishihara S, Uchino M, Ikeuchi H, Okabayashi K, Futami K, et al. Clinical features and oncological outcomes of intestinal cancers associated with ulcerative colitis and Crohn's disease. *J Gastroenterol*. 2023;58(1):14-24.
15. Nozawa H, Sasaki K, Emoto S, Murono K, Yokoyama Y, Sonoda H, et al. Benefits of a laparoscopic approach for second colorectal resection after colectomy or proctectomy -a retrospective study. *BMC Surg*. 2023;23(1):216.
16. Nozawa H, Taira T, Sonoda H, Sasaki K, Murono K, Emoto S, et al. Enhancement of radiation therapy by indoleamine 2,3 dioxygenase 1 inhibition through multimodal mechanisms. *BMC Cancer*. 2023;23(1):62.
17. Nozawa H, Yokota Y, Emoto S, Yokoyama Y,

- Sasaki K, Murono K, et al. Unexplained increases in serum carcinoembryonic antigen levels in colorectal cancer patients during the postoperative follow-up period: an analysis of its incidence and longitudinal pattern. *Ann Med*. 2023;55(2):2246997.
18. Okamoto K, Nozawa H, Emoto S, Murono K, Sasaki K, Ishihara S. Does statin suppress oxaliplatin-induced peripheral neuropathy in patients with colorectal cancer? A single-center observational study. *Support Care Cancer*. 2023; 31(12):660.
 19. Okamoto K, Nozawa H, Sonoda H, Kaneko M, Ishihara S. Combinatory anti-tumor activities of 1,4-bis[2-(dimethylamino)ethylamino]-5,8-dihydroxyanthracene-9,10-dione (AQ4) and temsirolimus against colorectal cancer cells. *J Cancer Res Clin Oncol*. 2023;149(8):4689-99.
 22. Ozaki K, Sasaki K, Abe H, Nozawa H, Murono K, Emoto S, et al. Apoptosis-related Prognostic Factors in Advanced Colorectal Cancer Determined Using Tissue Microarrays. *Anticancer Res*. 2023;43(9):3935-42.
 21. Yokoyama Y, Nozawa H, Sasaki K, Murono K, Emoto S, Matsuzaki H, et al. Essential anatomy for lateral lymph node dissection. *Ann Coloproctol*. 2023;39(6):457-66.
 22. Abe K, Anzai H, Eguchi S, Ikemura M, Shinozaki-Ushiku A, Shinagawa T, et al. Metastasis of Ovarian Cancer to the Descending Colon. *Case Rep Gastroenterol*. 2023;17(1):129-36.
 23. Abe K, Emoto S, Sasaki K, Nozawa H, Yasunaga Y, Ishihara S. Multiple ulcers and perforation of small intestine with everolimus use in a patient with rectal neuroendocrine tumor: A case report. *Int J Surg Case Rep*. 2023;106:108094.
 24. Kasuga S, Abe S, Nozawa H, Sasaki K, Murono K, Emoto S, et al. Diverticular perforation of terminal ileum associated with chemotherapy for non-small cell lung carcinoma: a case report. *J Surg Case Rep*. 2023;2023(4):rjad179.
 25. Kikuchi R, Emoto S, Nozawa H, Sasaki K, Murono K, Abe S, et al. Jejunal intussusception and perforation due to enteric muco-submucosal elongated polyp: a case report and literature review. *Surg Case Rep*. 2023;9(1):4.
 26. Komatsu K, Nozawa H, Sonoda H, Abe S, Emoto S, Murono K, et al. Colectomy, especially right hemicolectomy, is a possible predisposing factor of omental torsion. *ANZ J Surg*. 2023;93(12):3006-7.
 27. Yokose S, Murono K, Nozawa H, Sasaki K, Emoto S, Matsuzaki H, et al. Preoperative Simulation of Ileal Pouch-Anal Anastomosis in Patients With Ulcerative Colitis Using a 3-Dimensional Printed Model. *Inflamm Bowel Dis*. 2023;29(12):1865-70.
 28. Yokoyama Y, Ishibashi R, Fujishiro M, Ishihara S. The transnasal decompression tube versus self-expanding metallic stents for right-sided obstructive colorectal cancer. *Asian J Surg*. 2023; 46(4):1612-4.

Department of Vascular Surgery

Associate Professor and Chief of Vascular Surgery

Katsuyuki Hoshina, M.D., Ph.D.

Lecturer

Toshio Takayama, M.D., Ph.D.

Assistant Professor

Takuro Shirasu, M.D., Ph.D., Masaru Kimura, M.D., Ph.D.,

Kazuhiro Miyahara, M.D., Ph.D.

Homepage <https://vascular-1su.jp/>

Introduction and Organization

In 1995, a new system for postgraduate education was introduced. The First Department of Surgery was reorganized to form the Department of Vascular Surgery and the Department of Surgical Oncology. The staff of the Department of Vascular Surgery consists of one Associate Professor, one Lecturer, and three Assistant Professors. The outpatient office is located on the third floor of the Outpatient Building. The ward is situated on the eighth floor of the Ward Building. The administrative office and research laboratories are located in the Administration and Research Building. Current activities of the Department of Vascular Surgery in clinical practice, education, and research are summarized as follows.

Clinical activities

The Department of Vascular Surgery has an extensive clinical program in both primary and tertiary care for vascular problems, and manages patients with peripheral arterial occlusion, abdominal and thoraco-abdominal aortic aneurysms, peripheral aneurysm, visceral arterial occlusion, carotid artery disease and common disorders of the venous circulation such as varicose veins and venous leg ulcers. State-of-the-art techniques of percutaneous transluminal angioplasty, angioscopy and intraoperative ultrasonography are available for the treatment of peripheral arterial

disease. And endovascular aneurysm repair was also available for the treatment of abdominal aortic aneurysm. The outpatient clinic is open from Monday through Friday, and twenty-four-hour consultation is available for urgent or emergency problems.

Included in the department is the non-invasive Clinical Vascular Laboratory, which sees over 500 patients per year, with broad reaching expertise in peripheral vascular diagnostic modalities. Also the department has an active angiography program, which encompasses all aspects of diagnostic and therapeutic intervention in over 500 patients per year and a full range of other support and collaborative services.

On Monday, Wednesday and Friday mornings, pre- and post-surgery conferences are held. Operating days are Monday, Tuesday and Thursday. The vascular clinical conference is held every Tuesday evening.

Teaching activities

The operative procedure should be the basics of surgery. In 2017, the Japanese Board of Cardiovascular Surgery announced that 30 hours of Off JT experience will be required for new cardiovascular specialist applicants. Responding to this announcement and taking into consideration the social request for change in recent years, The Japanese Society for Vascular Surgery created the Off JT working group to create a new framework for Off JT. Thus far, there has

not been a versatile Off JT system that can be used in any institution with young surgeons. Therefore, in our department, we aimed to develop a simple and inexpensive Off JT system that can be used at any institution with medical students and young surgeons. We developed a new Off JT system that is simple and inexpensive and can be used at any institution with medical students and young surgeons. The effectiveness and appropriateness of this system were confirmed by the learning curve, analysis of the balance of the anastomosis, and scoring by the trainers. In addition, we demonstrated the relationships among time, performance, and skill. We will set this system as one of the educational methods for surgeons.

The Department of Vascular Surgery also offers a fellowship in vascular surgery for well-qualified surgeons who have completed their training in general surgery and wish to further specialize in vascular surgery. The Department of Vascular Surgery has a Vascular Surgery Training Program and provides broad reaching experience in technical aspects of vascular surgery, development of surgical judgment, and increasing knowledge about routine and complex conditions. In addition, the dedicated staff offers multiple opportunities for academic development both along clinical and basic scientific lines.

In the undergraduate education program, the Department of Vascular Surgery plays a role in the systemic and clinical lectures and the bedside learning program for 3rd year medical students, in cooperation with other departments of surgery. In the postgraduate education program, new residents are trained to become qualified surgeons in our department. The Department of Vascular Surgery is involved with the education program of the post-graduate education meeting, which is held monthly. In addition to pre- and post-surgery clinical conferences, the residents are expected to attend research conferences and seminars, which are held periodically.

Research activities

The Department of Vascular Surgery includes major research laboratories for academic development both along clinical and basic scientific lines. The clinical vascular laboratories are approaching completely non-invasive testing for vascular disorders, analyzing

essential physiologic information about the specific problems being addressed. The basic vascular laboratories are actively performing research on endothelial biology, the mechanism of intimal hyperplasia, microcirculation, application of gene therapy to vascular surgery and vascular prosthesis development. Vascular research meeting is held every month on Saturday morning. The following are the major themes under research.

- 1) Navigation system for less invasive vascular surgery
- 2) Pathophysiology of the development of the aneurysm
- 3) Pathophysiology of stent restenosis
- 4) Analyzing the intercellular transmission of the growth signal in the vascular smooth muscle cells
- 5) Tissue oxygen dynamics assessed by near infrared spectroscopy
- 6) Genome wide-association studies for arteriosclerosis.
- 7) Pharmacological analysis of microcirculation in in-vivo model
- 8) Mechanism of arteriogenesis in ischemic limb.
- 9) Development of a new drug delivery system for therapeutic angiogenesis
- 10) Hemodynamic analysis after endovascular aneurysm repair
- 11) Introduction of gene into vascular wall cells by electroporation
- 12) Application of nano technology for in-vivo gene transfer to vascular wall cells
- 13) Basic research for arterialization of artificial organ
- 14) Development of a new method for evaluation of limb ischemia
- 15) Development of a new machine for auto-evaluation of in-vivo endothelial function
- 16) Creating strategy for diagnosis of acute aortic syndrome.
- 17) Analysis of ambulatory system and muscle mechanics in claudicants with peripheral artery disease.
- 18) Modeling of saccular aneurysm with the computational simulation.
- 19) Development of hemostatic agent using Tetra-PEG hydrogel.
- 20) Prediction of dilated morphology of aortic

aneurysm by airbag simulation.

- 21) Quantification of hand movements during suture using Leap Motion and its clinical feedback.
- 22) Study of intimal hyperplasia using aorta-inferior vena cava fistula model.

References

1. Endo T, Takayama T, Kimura M, Mochizuki Y, Taniguchi R, Hoshina K. A case of endovascular treatment for iatrogenic left vertebral artery injury due to central line catheter placement. *J Vasc Surg Cases Innov Tech.* 2023;10:101368.
2. Matsubara K, Taniguchi R, Shirasu T, Miyahara K, Mochizuki Y, Takayama T, Hoshina K. Giant coeliac artery aneurysm treated with a hybrid approach: A case report. *EJVES Vasc Forum.* 2023;61:16-19.
3. Nagita H, Wang C, Saigusa H, Hoshina K, Suhara M, Oshima M. Deformed popliteal artery due to highly flexed knee position can cause kinks, creating an unfavorable hemodynamic state. *Circ J* 2023;88:351-8
4. Endo T, Miyahara K, Shirasu T, Mochizuki Y, Taniguchi R, Takayama T, Hoshina K. Risk factors for incisional hernia after open abdominal aortic aneurysm repair. *In Vivo.* 2023;37:2803-2807.
5. Maeno R, Taniguchi R, Suhara M, Mochizuki Y, Takayama T, Hoshina K. Area reduction of perforation with a small-size sheath technique for iatrogenic femoral artery pseudoaneurysm with a large perforation. *J Vasc Surg Cases Innov Tech.* 2023 May 25;9(3):101235.
6. Endo T, Takayama T, Suhara M, Mochizuki Y, Taniguchi R, Hoshina K. A case of popliteal artery rupture in an 11-year-old patient with vascular Ehlers-Danlos syndrome. *J Vasc Surg Cases Innov Tech.* 2023 Feb 22;9(2):101129.
7. Miyata T, Kumamaru H, Mii S, Kinukawa N, Miyata H, Shigematsu K, Azuma N, Ishida A, Izumi Y, Inoue Y, Uchida H, Ohki T, Kuma S, Kurosawa K, Kodama A, Komai H, Komori K, Shibuya T, Shindo S, Sugimoto I, Deguchi J, Hoshina K, Hideaki M, Midorikawa H, Yamaoka T, Yamashita H, Yunoki Y. Corrigendum to "Prediction models for two-year overall survival and amputation free survival after revascularization for chronic limb threatening ischemia. [Volume 64, Issue 4, October 2022, Pages 367-76]". *Eur J Vasc Endovasc Surg.* 2023 Apr; 65(4):616.
8. Hoshina K, Suhara M, Miyahara K, Mochizuki Y, Taniguchi R, Takayama T; Japan AFX registry. Midterm outcomes of AFX2 endografts used in combination with aortic cuffs. *J Vasc Surg.* 2023 Feb;77(2):424-431.e1.

Department of Breast and Endocrine Surgery

Professor

Yasuyuki Seto M.D., Ph.D.

Associate Professor

Masahiko Tanabe M.D., Ph.D.

Lecturer

Kotoe Nishioka M.D., Ph.D.

Associates

Ayaka Sato M.D., Ph.D.

Asako Sasahara M.D., Ph.D.

Arisa Morizono M.D., Ph.D.

Satoshi Yamashita M.D., Ph.D.

※The following information is the same as that of the previous year for certain reasons.

Homepage

Organization

Our section is staffed by one professor, associate professor, lecturer, and four associates. Official activities of our units are run on the same schedule as the Department of Gastrointestinal Surgery.

Clinical Activities

We started our activities in this area in 1987, and our department was established with the reconstruction of our hospital structure in 1997. This is a result of the growth of demand nationally and internationally. It is caused by not only treatment for the malignant disease but also functional one or giving more attention to the quality of life.

Professional skills and broader knowledge of the endocrine system are required for this area. Diseases we treat at our department are breast, thyroid, and parathyroid. In addition to treatment for malignant cases of these diseases, we perform surgical procedures as well as systemic therapy. We co-work with the department of internal endocrine medicine and

have about 250 surgical procedures annually.

In breast surgery, more than half of mammary cancer patients undergo breast-preserving surgery. In addition, sentinel node navigation surgery has been adopted, resulting in better postoperative life quality. Reconstruction surgery for breast cancer is likely to provide much better QOL. In this field, we have collaborated with the Department of Plastic Surgery. Chemotherapy, hormone therapy, and molecular targeting therapy play essential roles in breast cancer treatment. We have accumulated a lot of experience and achievement in this field.

Our clinical themes are 1) establishment of safe procedures for endocrine surgery without complications; 2) diagnosis and treatment of micro-breast lesions under ultrasonographic guides; 3) preoperative diagnosis for thyroid neoplasms and breast tumors.

Research Activities

We investigate broad areas of breast cancer, thyroid

disease, and parathyroid disease. Most of our studies are performed with other good institutions.

- 1) Hereditary Breast and Ovarian Cancer syndrome
- 2) Precision medicine based on Todai OncoPanel
- 3) Clinical significance of Ki67 in the area of early breast cancer.
- 4) Clinical evaluation for the developing drugs in breast and thyroid cancer.
- 5) Studies in the area of sentinel node biopsy in breast cancer.
- 6) Studies about the management of the toxic effects of chemotherapies.
- 7) Cover makeup studies for cancer patients.
- 8) Epigenetic changes critical for breast cancer development.
- 9) Cancer stem cells in breast cancer.
- 10) Quantification of HER2 expression using Digital PCR.
- 11) Development of molecular target drugs in the area of TGF beta
- 12) Analysis of MED12 mutation and TERT promoter mutation in breast fibroadenoma and phyllodes tumor.
- 13) Loss of BRCA1 expression and morphological features associated with BRCA1 promoter methylation status in triple-negative breast cancer.
- 14) Epidemiological study using nationwide databases to resolve clinical questions

Publications

1. Konishi T, Fujiogi M, Shigemi D, Matsui H, Fushimi K, Tanabe M, Seto Y, Yasunaga H. Risk Factors for Postoperative Bleeding Following Breast Cancer Surgery: A Nationwide Database Study of 477,108 Cases in Japan *World J Surg.* 2022 Dec;46(12):3062-3071.
2. Niwa T, Konishi T, Sasahara A, Sato A, Morizono A, Harada M, Nishioka K, Fukuoka O, Makise N, Saito Y, Ando M, Yoshimoto T, Shikama T, Yamashita S, Tanabe M, Seto Y. Subcutaneous axillary primary epithelioid hemangioendothelioma: report of a rare case. *Surg Case Rep.* 2022 Sep 9;8(1):166.
3. Konishi T, Goto T, Fujiogi M, Michihata N, Kumazawa R, Matsui H, Fushimi K, Tanabe M, Seto Y, Yasunaga H. New machine learning scoring system for predicting postoperative mortality in gastroduodenal ulcer perforation: A study using a Japanese nationwide inpatient database. *Surgery.* 2022 Apr;171(4):1036-1042.
4. Konishi T, Fujiogi M, Michihata N, Morita K, Matsui H, Fushimi K, Tanabe M, Seto Y, Yasunaga H. Association of Operative Day of the Week with the Length of Stay and Total Hospitalization Costs in Patients with Partial Mastectomy: A Nationwide Database Study in Japan. *JMA J.* 2022 Jul 15;5(3):319-327.
5. Konishi T, Fujiogi M, Shigemi D, Nishioka K, Matsui H, Fushimi K, Tanabe M, Seto Y, Yasunaga H. Surgical and obstetric outcomes of breast cancer surgery during pregnancy: a nationwide database study in Japan. *Breast Cancer Res Treat.* 2022 Oct;195(3):289-299.
6. Konishi T, Takamoto T, Fujiogi M, Hashimoto Y, Matsui H, Fushimi K, Tanabe M, Seto Y, Yasunaga H. Laparoscopic versus open distal pancreatectomy with or without splenectomy: A propensity score analysis in Japan. *Int J Surg.* 2022 Aug;104:106765.
7. Konishi T, Fujiogi M, Michihata N, Ohbe H, Matsui H, Fushimi K, Tanabe M, Seto Y, Yasunaga H. Cost-effectiveness analysis of trastuzumab monotherapy versus adjuvant chemotherapy plus trastuzumab in elderly patients with HER2-positive early breast cancer. *Jpn J Clin Oncol.* 2022 Oct 6;52(10):1115-1123.
8. Konishi T, Fujiogi M, Michihata N, Matsui H, Tanabe M, Seto Y, Yasunaga H. Association between body mass index and incidence of breast cancer in premenopausal women: a Japanese nationwide database study. *Breast Cancer Res Treat.* 2022 Jul;194(2):315-325.
9. Konishi T, Yoshimoto T, Fujiogi M, Yamana H, Tanabe M, Seto Y, Yasunaga H. Validity of operative information in Japanese administrative data: a chart review-based analysis of 1221 cases at a single institution. *Surg Today.* 2022 Oct;52(10):1484-1490.
10. Konishi T, Fujiogi M, Michihata N, Kumazawa R, Ohbe H, Matsui H, Fushimi K, Ogita M, Tanabe M, Seto Y, Yasunaga H. Interstitial lung disorders following postoperative radiotherapy with

concurrent or sequential hormonal therapy for breast cancer: a nationwide database study in Japan. *Breast Cancer*. 2022 Jul;29(4):688-697.

11. Konishi T, Fujiogi M, Tanabe M, Seto Y, Yasunaga H. ASO Author Reflections: Neoadjuvant Chemotherapy Does Not Affect Short-Term Outcomes After Breast Cancer Surgery. *Ann Surg Oncol*. 2022 May;29(5):3011-3012.
12. Konishi T, Fujiogi M, Sato A, Michihata N, Kumazawa R, Matsui H, Fushimi K, Tanabe M, Seto Y, Yasunaga H. Short-Term Outcomes Following Breast Cancer Surgery With and Without Neoadjuvant Chemotherapy: A Nationwide Administrative Database Study in Japan. *Ann Surg Oncol*. 2022 May;29(5):3000-3010.
13. Konishi T, Fujiogi M, Michihata N, Niwa T, Morita K, Matsui H, Fushimi K, Tanabe M, Seto Y, Yasunaga H. Impact of body mass index on short-term outcomes after differentiated thyroid cancer surgery: a nationwide inpatient database study in Japan. *Eur Thyroid J*. 2022 Jan 1;11(1):e210081.

Surgical Sciences

2. Sensory and Motor System Medicine

Department of Dermatology

Professor

Shinichi Sato, M.D., Ph.D.

Associate Professor

Sayaka Shibata, M.D., Ph.D.

Hayakazu Sumida, M.D., Ph.D.

Lecturer

Takuya Miyagawa, M.D., Ph.D.

Takashi Yamashita, M.D., Ph.D.

Daisuke Yamada, M.D., Ph.D.

Asako Yoshizaki, M.D., Ph.D.

Hospital Lecturer

Shunsuke Miura, M.D., Ph.D.

Associate

Hikari Boki, M.D., Ph.D.

Jun Omatsu, M.D., Ph.D.

Ai Kuzumi, M.D., Ph.D.

Satoshi Toyama, M.D., Ph.D.

Teruyoshi Hisamoto, M.D., Ph.D.

Kazuki Matsuda, M.D., Ph.D.

Website <https://dermatology.m.u-tokyo.ac.jp/>

Introduction and Organization

The Department of dermatology celebrated its 100th anniversary in 1990. Originally it was founded as the Department of Dermatology and Urology, which also encompassed venereology. In 1946, the Department of Dermatology was separated from that of Urology. Regarding venereology, sexually transmitted diseases only related to skin manifestations are now dealt with in our department.

As of March 2023, the professor, one associate professor, five lecturers, two hospital lecturers and seven associates take part in inpatient and outpatient cares as well as research and teaching activities. Fifty-two doctors who basically belong to our department are currently out in affiliated hospitals mainly engaged in clinical works there. Additionally, three staff members are abroad at present, mainly involved in advanced research activities in cell biology and molecular biology.

Clinical Activities

In the outpatient clinic we see around 200 patients a day. Incisional and excisional biopsies are frequently performed under local anesthesia at the outpatient operation facilities belonging to our department. Clinical and histological discussions by all staff members including Professor and Associate Professors are held regularly, which always gives us invaluable lessons.

Concerning the inpatient clinic, there are about ten staff members under the supervision of the ward-chief. Surgical operations such as removal of malignancies and skin grafting that require general anesthesia are also performed weekly in the central surgical facilities.

Education

We have twenty dermatologists who are studying in the postgraduate course under the guidance of staff members of our department.

In addition to series of lectures, clinical education is provided for fifth- and sixth- grade medical students, which aims at giving a general introduction for how to make dermatological approaches for diagnosis and treatment, with a stress on learning how to observe and describe a variety of skin eruptions. Actually the students are supposed to see patients in outpatient clinic every day for an entire week, as well as to participate in the inpatient clinic.

Research

Each specialized outpatient service reflects its own research field in a disease-oriented manner. However, those specialized groups performing their own clinical and research activities are never exclusive, and there are increasing communications with other departments such as internal medicine and blood transfusion service as well as intergroup communications. Recent advanced techniques in cellular, molecular biology and our newly established laboratories, will enable us to organize optimal research conditions.

Publications

1. Ai Kuzumi, Daisuke Yamada, Jun Omatsu, Naomi Takahashi-Shishido, Shinichi Sato. Squamous cell carcinoma arising in the irradiated field more than 60 years after radiotherapy for a giant congenital melanocytic nevus. *Annals of Dermatology*. 2023;35(1):134-139.
2. Okuto Iwasawa, Koji Kamiya, Hirofumi Okada, Takeo Maekawa, Mayumi Komine, Mamitaro Ohtsuki. Diagnostic difficulties in secondary syphilis: A case report. *International Journal of Dermatology*. 2023;62(2):e59-e61.
3. Kenta Oka, Takuya Miyagawa, Hiraku Suga, Tomomitsu Miyagaki, Yuka Mizuno, Hiroaki Kamijo, Teruyoshi Hisamoto, Issei Omori, Hikari Boki, Tomonori Oka, Naomi Takahashi-Shishido, Makoto Sugaya, and Shinichi Sato. Increased Expression of Squamous Cell Carcinoma Antigen 1 and 2 in Mycosis Fungoides and Sézary Syndrome. *European Journal of Dermatology*. 2022;32(4):464-470.
4. Hiroki Yamamoto, Koji Kamiya, Hirofumi Okada, Takeo Maekawa, Mayumi Komine, Mamitaro Ohtsuki. A case of acrodermatitis continua of Hallopeau evolving into generalized pustular psoriasis successfully treated with guselkumab. *Int J Dermatol*. 2023;62(2):269-270.
5. Yuka Mizuno, Sayaka Shibata, Tomomitsu Miyagaki, Yukiko Ito, Haruka Taira, Issei Omori, Teruyoshi Hisamoto, Kenta Oka, Kazuki M Matsuda, Hikari Boki, Naomi Takahashi-Shishido, Makoto Sugaya, Shinichi Sato. Serum cell-free DNA as a new biomarker in cutaneous T-cell lymphoma. *The Journal of Dermatology*. 2022;49(11):1124-1130.
6. Ai Kuzumi, Ayumi Yoshizaki, Shunki Mitsuo, Tomomi Miyake, Shinichi Sato. Tocilizumab-induced organizing pneumonia in a patient with systemic sclerosis-associated interstitial lung disease. *Rheumatology*. 2023;62(SI):SI143-SI144.
7. Norimatsu Y, Yoshizaki A, Yamada T, Akiyama Y, Toyama S, Sato S. Pemphigus vulgaris with advanced hypopharyngeal and gastric cancer following SARS-CoV-2 vaccination. *The Journal of Dermatology*. 2023;50(2):e74-e75.
8. Akatsuka T, Omatsu J, Miyagawa T, Omori I, Kawashima H, Oshima N, Sato S. Congenital midline sinus of the upper lip: evaluating the use of ultrasonography. *Skin Health and Disease*. 2022;3(1):e170.
9. Yuka Mizuno, Sayaka Shibata, Yukiko Ito, Haruka Taira, Eiki Sugimoto, Kentaro Awaji, Shinichi Sato. IL-26-DNA complexes promote inflammation and dermal-epidermal separation in a modified human cryosection model of bullous pemphigoid. *Frontiers in Immunology*. 2022;13:1013382.
10. Sayaka Shibata. Epigenetic control of skin immunity. *Immunological Medicine*. 2023;46(2):62-68.
11. Daisuke Yamada, Simon Vu, Xuesong Wu, Zhenrui Shi, Desiree Morris, Joshua D. Bloomstein, Mindy Huynh, Jie Zheng, Samuel T Hwang. Gain-of-Function of TRPM4 Predisposes Mice to Psoriasiform Dermatitis. *Frontiers in Immunology*. 2022;13:1025499.
12. Takemichi Fukasawa, Satoshi Toyama, Atsushi Enomoto, Asako Yoshizaki-Ogawa, Yuta Norimatsu, Shoko Tateishi, Hiroko Kanda, Kiyoshi Miyagawa, Shinichi Sato, and Ayumi

- Yoshizaki. Utility of nailfold capillary assessment for predicting psoriatic arthritis based on a prospective observational cohort study. *Rheumatology*. 2023;62(7):2418-2425.
13. Taro Akatsuka, Tetsuo Toyama, Sohshi Morimura, Mina Komuta, Ichiro Mori, Tatsuya Tanaka, Yusuke Tabei, Masatou Kawashima, Akira Matsuno, Makoto Sugaya. A case of primary meningeal melanocytosis treated with combination therapy with nivolumab and ipilimumab. *The Journal of Dermatology*. 2023; 50(4):e125-e126.
 14. Hayakazu Sumida, Yoshihide Asano, Jun Shimizu, Shinichi Sato. Edema localized to the lips as a novel manifestation of myositis. *International Journal of Rheumatic Diseases*. 2023;26(4):789-792.
 15. Ai Kuzumi, Satoshi Ebata, Takemichi Fukasawa, Kazuki M Matsuda, Hirohito Kotani, Asako Yoshizaki-Ogawa, Shinichi Sato, Ayumi Yoshizaki. Long-term efficacy of rituximab in systemic sclerosis: follow-up of the DESIRES trial with a focus on serum immunoglobulin levels. *JAMA Dermatology*. 2023;159(4):374-383.
 16. Shunsuke Miura, Sandra Garcet, Xuan Li, Inna Cueto, Charissa Salud-Gnilo, Norma Kunjravia, Kazuhiko Yamamura, Juana Gonzalez, Mika Murai-Yamamura, Darshna Rambhia, and James G. Krueger. Cathelicidin Antimicrobial Peptide LL37 Induces TLR8 and Amplifies IL-36 γ and IL-17C in Human Keratinocytes. *Journal of Investigative Dermatology*. 2023;143(5):832-841.
 17. Teruyoshi Hisamoto, Hiraku Suga, Asako Yoshizaki-Ogawa, Shinichi Sato, Ayumi Yoshizaki. Increased Serum Levels of Tumor Necrosis Factor-like Ligand 1A in Atopic Dermatitis. *International Journal of Molecular Sciences*. 2023;24(3):1813.
 18. Shunsuke Miura, Yohei Ichimura, Uri Sela, Sandra Garcet, Charissa Salud-Gnilo, Xuan Li, Juana Gonzalez, Mika Murai-Yamamura, Kazuhiko Yamamura, Darshna Rambhia, Norma Kunjravia, and James G Krueger. *Staphylococcus Aureus* and *Streptococcus Pyogenes* Induce Psoriasis-Related Transcriptomes Augmented by IL-17A and TNF- α . *Journal of Investigative Dermatology*. 2023;143(8):1613-1617.
 19. Kazuki M. Matsuda, Ayumi Yoshizaki, Ai Kuzumi, Satoshi Toyama, Kentaro Awaji, Tomomi Miyake, Shinichi Sato*. Rapid improvement of systemic sclerosis-associated intestinal pseudo-obstruction with intravenous immunoglobulin administration. *Rheumatology*. 2023;62(9):3139-3145.
 20. Takemichi Fukasawa, Ayumi Yoshizaki, Satoshi Ebata, Maiko Fukayama, Ai Kuzumi, Yuta Norimatsu, Kazuki M. Matsuda, Hirohito Kotani, Hayakazu Sumida, Asako Yoshizaki-Ogawa, Hisashi Kagebayashi, Shinichi Sato. Interleukin-17 pathway inhibition with brodalumab in early systemic sclerosis: analysis of a single-arm, open-label, phase 1. *Journal of the American Academy of Dermatology*. 2023;89(2):366-369.
 21. Omori I, Sumida H, Sugimori A, Sakakibara M, Urano-Takaoka M, Iwasawa O, Saito H, Matsuno A, Sato S. Serum cold-inducible RNA-binding protein levels as a potential biomarker for systemic sclerosis-associated interstitial lung disease. *Sci Rep*. 2023;13(1):5017.
 22. Takemichi Fukasawa, Atsushi Enomoto, Asako Yoshizaki-Ogawa, Shinichi Sato, Kiyoshi Miyagawa, Ayumi Yoshizaki .The role of STK38 in DNA damage response and its application of radio-sensitization. *Cancers*. 2023;15(7):2054.
 23. Yuta Norimatsu, Taeko Goto, Asako Kogure, Yoshihiro Kuwano. Chemical burns generated by chlorine gas. *JEADV Clinical Practice*. 2023; 2(2):341-342.
 24. Purevsuren M, Uehara M, Ishizuka M, Suzuki Y, Shimbo M, Kakuda N, Ishii S, Sumida H, Miyazaki M, Yamashita T, Yoshizaki A, Asano Y, Sato S, Hatano M, Komuro I. Native T1 mapping in early diffuse and limited systemic sclerosis, and its association with diastolic function. *J Cardiol*. 2023;82(2):100-107.

Department of Plastic and Reconstructive Surgery

Professor

Mutsumi Okazaki, M.D.

Associate Professor

Shimpei Miyamoto, M.D.

Lecturer

Yoko Tomioka, M.D.

Project Lecturer

Koji Kanayama, M.D.

Associate

Kou Fujisawa, M.D., Jun Oba, M.D., Rui Yang, M.D., Daichi Kurita M.D.

Homepage <https://plastic.m.u-tokyo.ac.jp/english/>

Organization

The present faculty of the Department of Plastic and Reconstructive Surgery consists of 1 professor, 1 associate professor, 1 project lecturer, 1 project lecturer, 4 associates, 5 physicians, and 5 residents. There are about 100 doctors in the department, but most are serving in rotation at affiliated hospitals.

The outpatient clinic is located on the 3rd floor of the outpatients building, while there are wards with about 16 available beds on the 10th floor in the New Ward. Our faculty room is located in the Medical Laboratory Building and laboratory rooms in the East Laboratory Building.

The present status of the educational, research and clinical activities of the department is as follows.

Clinical Activities

The outpatient clinic is opened every morning from Monday to Friday. There are several specialized clinics for facial paralysis, breast reconstruction, head and neck reconstruction, congenital anomalies, vascular malformations, critical limb ischemia,

lymphedema, keloid, abdominal hernia, and cosmetic surgery including cosmetic dermatology. Over 1,000 new patients visited our department, including about 800 patients in emergency. About 1,400 surgeries were performed. Each week, preoperative and postoperative conferences that all members of the department should attend are held on Tuesday and Wednesday evening respectively.

Teaching Activities

In regard to pregraduate education, the department has the duty of lecturing to 2nd and 4th year medical students, and also of instructing 4th medical students in bed side practice. The subjects taken up in the lectures include general concepts of plastic surgery, wound healing, congenital malformations, skin grafts and flaps, microsurgery, head and neck reconstruction, hand surgery, craniomaxillofacial surgery, burn and trauma, cosmetic surgery, and regenerative medicine. In the bed side practice the students have the opportunity of seeing various diseases and disorders in the field of plastic surgery and attending inpatients

and surgical operations and clinical lectures by faculty members. For graduate school students, microsurgical training program is undertaken in the laboratory room. In the postgraduate course, after completing the 6-year training program, a trainee can sit for the board examination of the Japan Society of Plastic and Reconstructive Surgery.

Research Activities

Basic and clinical researches are performed in groups. The major research subjects are as follows:

- 1) Blink examination for appropriate closing-eye function in patients with facial paralysis.
- 2) Studies on monitoring tissue circulation using flexible optical probe.
- 3) ICG examination for evaluating blood and lymph flow.
- 4) In vivo reprogramming of wound-resident cells generates skin epithelial tissue
- 5) Clinical studies on fat regeneration using suctioned fat tissue and adipose stromal progenitor cells.
- 6) Studies on hair regrowth using epidermal stem cells, dermal papilla cells and dermal sheath cells.
- 7) Basic studies on free tissue transfer using microsurgery.

References (2023)

1. Hongo H, Miyawaki S, Teranishi Y, Mitsui J, Katoh H, Komura D, Tsubota K, Matsukawa T, Watanabe M, Kurita M, Yoshimura J, Dofuku S, Ohara K, Ishigami D, Okano A, Kato M, Hakuno F, Takahashi A, Kunita A, Ishiura H, Shin M, Nakatomi H, Nagao T, Goto H, Takahashi SI, Ushiku T, Ishikawa S, Okazaki M, Morishita S, Tsuji S, Saito N. Somatic GJA4 gain-of-function mutation in orbital cavernous venous malformations. *Angiogenesis*. 2023 Feb;26(1):37-52.
2. Fujisawa K, Kurita M, Yamashita S, Miyamoto S, Iida T, Okazaki M. A nationwide online survey of current trends in microsurgical practice among Japanese plastic surgeons. *Microsurgery*. 2023 Mar;43(3):302-303.
3. Takeishi H, Miyamoto S, Tomioka Y, Kanayama K, Okazaki M. Nasal alar reconstruction using the free auricular helix flap based on the flow-through concept: Report of two cases. *Microsurgery*. 2023 May;43(4):392-396.
4. Kato M, Ishikawa S, Shen Q, Du Z, Katashima T, Naito M, Numahata T, Okazaki M, Sakai T, Kurita M. In situ-formable, dynamic crosslinked poly(ethylene glycol) carrier for localized adeno-associated virus infection and reduced off-target effects. *Commun Biol*. 2023 May 16;6(1):508.
5. Miyamoto S, Fujisawa K, Okazaki M. Preoperative Peroneal Artery Perforator Mapping Using Indocyanine Green Angiography: A Prospective Clinical Trial. *Plast Reconstr Surg*. 2023 Jun 1;151(6):1051e-1053e.
6. Shiraishi M, Narushima M, Banda CH, Mitsui K, Danno K, Ishiura R, Kurita M, Yuzuriha S, Okazaki M. Safety of SARS-CoV-2 Vaccination in Patients with Vascular Malformations: Patient-Reported Adverse Vaccine Reactions. *Ann Vasc Dis*. 2023 Jun 25;16(2):101-107.
7. Chang J, Miyamoto S, Okazaki M. Small saphenous vein interposition graft in free fibular flap transfer for mandibular reconstruction in a patient. *Microsurgery*. 2023 Jul;43(5):529-530.
8. Fujisawa K, Miyamoto S, Kobayashi H, Okazaki M. Vascularized Fibular Grafts for Failed Liquid Nitrogen-treated Autografts in the Humerus: Report of Two Cases. *Plast Reconstr Surg Glob Open*. 2023 Aug 4;11(8):e5166.
9. Hidaka T, Tanaka K, Minami M, Mori H, Okazaki M. Risk Factors for Postoperative Infection After Maxillary Reconstruction Using Skeletal Grafts. *J Craniofac Surg*. 2023 Oct 1;34(7):e649-e651.
10. Matsumoto N, Kashio A, Yoshida M, Kondo K, Miyamoto S, Okazaki M, Ikemura M, Ushiku T, Yamasoba T. Cholesterol granuloma in facial nerve canal presenting with facial nerve paralysis. *Auris Nasus Larynx*. 2023 Oct;50(5):799-804.
11. Tomioka Y, Okazaki M, Kurita M, Fujisawa K, Matsutani H. Stair-Step Incision for Composite Grafts in Nasal Reconstruction. *J Craniofac Surg*. 2023 Nov-Dec 01;34(8):2464-2467.
12. Kanayama K, Tanioka M, Hattori Y, Iida T, Okazaki M. Long-term survival of the Sister Mary Joseph nodule originating from breast

cancer: A case report. *World J Clin Cases*. 2023 Dec 6;11(34):8205-8211.

13. Tomioka YK, Okazaki M, Matsutani H. Split-thickness Plantar Skin Graft for Foot Syndactyly. *Plast Reconstr Surg Glob Open*. 2023 Dec 22;11(12):e5498.

Department of Oral-Maxillofacial Surgery

Professor

Kazuto Hoshi, M.D., Ph.D.

Associate Professor

Hideto Saijo, D.D.S., Ph.D.

Lecturer

Toru Ogasawara, D.D.S., Ph.D.

Hideyuki Suenaga, D.D.S., Ph.D.

Kazumi Ohkubo, D.D.S., Ph.D.

Masanobu Abe, D.D.S., Ph.D.

Associate

Natsuko Uchino, D.D.S., Ph.D.

Rika Narita, D.D.S., Ph.D.

Yusuke Tsuda, M.D., Ph.D.

Miki Kashiwagi, D.D.S., Ph.D.

Hiroshi Kawakami, D.D.S., Ph.D.

Asako Taniguchi, D.D.S., Ph.D.

Kenichi Kumagai, D.D.S., Ph.D.

Sanshiro Kanazawa, D.D.S., Ph.D.

Takao Uchiyama, D.D.S., Ph.D.

Homepage <http://plaza.umin.ac.jp/%7Eoralsurg/>

Introduction and Organization

Department of Oral and Maxillofacial Surgery, commenced by Dr. Hisashi Ishihara in 1900, is one of the oldest departments in Graduate School of Medicine, the University of Tokyo. This department consists of wide variety of specialists, such as oral surgeons, orthodontists and prosthodontists. We handle all diseases in the oral-maxillofacial region, such as congenital anomalies, jaw deformities, benign and malignant tumors, trauma and inflammation. In particular, we have established and practiced medical system for cleft lip and palate since around 2000. In November 2016, we established the Cleft Lip and Palate Center, which we become the center for oral surgeons, orthodontists, and others. Specialists such as prosthodontists, otolaryngologists, anesthesiologists, obstetricians, pediatricians, pediatric surgeons, speech therapists, nurses, dental hygienists, and dental

technicians form a team to deal with illnesses from all directions and provide multidisciplinary treatment. Dental care for the patients who have systemic disorders or under medical control is another field of our department. Multidisciplinary treatment teamed by these specialists is characteristic and has performed excellent results in clinical works. In research fields, all staffs participate in the clinical and basic research to support the treatment scientifically and to develop new treatment protocols, and we have mainly performed the experimental studies on the regenerative abilities of tissues such as bone, periosteum, cartilage, perichondrium, vessels, nerve, and skin. At present, we are focusing on tissue engineering in research works especially in bone, cartilage and vessels. The Department of Tissue Engineering was established at the University of Tokyo Hospital in October 2001, and at present Professor Kazuto Hoshi of our department is

concurrently serving as its director. The Department of Oral and Maxillofacial Surgery has Cartilage and Bone Regenerative Medicine and a Tissue Engineering Department, where assistant professors, and graduate students are conducting basic research on regenerative medicine in the maxillofacial region.

Clinical activities

In the outpatient clinic, we have 12 dental treatment booths, one operation room and one speech therapy room. Average number of patients treated at outpatient clinic is approximately 100 per day.

Our department has two sections mainly; one is oral and maxillofacial surgery and another is dental and orthodontic dentistry.

In outward dispensary, oral surgery section performs dental surgeries such as extraction of impacted teeth, amputation of infected dental root and gingivoplasty in the operation room. Patients who had been performed surgical treatment are also followed up after release from the hospital.

Dentistry and orthodontic dentistry performs facial growth control and tooth movements for patients with congenital orofacial anomalies such as cleft lip and palate, jaw deformities and other congenital deformities. Speech therapy for the patients with cleft lip and palate is also performed by speech therapists in our department.

Special section for patients of congenital deformities is on Monday afternoon examined by plastic surgeon, oral and maxillofacial surgeons, orthodontists. We also have special sections for patients with oral cancer and temporomandibular joint disorder.

In the ward, we have approximately 400 new inpatients and surgical treatment is performed on approximately 300 cases per year. The main surgical treatments are chiropasty and palatoplasty for cleft lip and palate patients, bone grafting in alveolar cleft, orthognatic surgery of orofacial deformities, fixation of orofacial fractures, resection of malignant tumors combined with reconstruction surgery.

Peculiarity of our treatment strategy is team approach that consists of oral and maxillofacial surgeons, orthodontists and prosthodontists. In our department, patients with congenital dento-facial deformity are treated by utilizing several techniques such as distrac-

tion technique, autologous bone graft technique, and the original artificial bone graft technique in addition to orthognatic surgery. The original bone graft is made from patient's three dimensional images of CT data and this technique is now applied for patients.

Education

Teaching activities are divided into two parts; for undergraduate medical students and for postgraduate dental students. For undergraduate students, we make 5 systematic lectures in their second year of specialized course, and one lecture and one week bedside learning in final year. Through these curriculums, we demonstrate the characteristics and treatments of the diseases in oral-maxillofacial region. Teaching is focused on following points; congenital anomalies such as cleft lip and palate and branchial arch syndromes, dentofacial deformities caused by developmental and acquired problems, surgical resection and functional reconstruction of benign and malignant tumors, temporomandibular joint disorders, inflammation and maxillofacial trauma. Minimum dental knowledge concerning jaw movement, tooth pain, periodontal disease, malocclusion and dental restorations are instructed.

For postgraduate dental students, we have two-year-resident course. This course aims to train for a wide range of dental treatments and to learn about medical cares. Various specialists instruct dental treatments for them in outpatient clinic. Dental caries treatments, periodontal cares and applications of dentures are instructed. Tooth extractions and orthodontic treatment are instructed by oral surgeons and orthodontists. Medical cares in the ward are taught by medical doctors and oral surgeons.

After two-year residential course, research training at postgraduate school is positively recommended. Our aim for education of clinician is to raise up specialists mastered both clinic and research skills.

Research

Our research project consists of clinic and basic sections. Each research themes are closely related on the aim of clinical improvement.

The main projects are as follows.

Clinical research:

1. Treatment of facial deformities and malocclusion in patients with cleft lip/ palate
2. Research on facial growth in patients with craniofacial anomalies
3. Reconstruction of oral and maxillofacial area by custom-made artificial bone (CT bone) (clinical trial)
4. Transplantation of implant-type tissue-engineered cartilage for cleft lip-nose patients
5. QOL study of oral health care system in preparative cancer patients
6. Overcoming eating loss (eat-loss)
7. The association between oral disorders and systemic diseases
8. Development of surgical assisted systems using artificial intelligence, computer vision, and augmented reality
9. Research on the treatment of temporo-mandibular joint disorder using autologous adipose-derived mesenchymal stem cells

Basic and experimental research:

1. Regeneration of bone and cartilage with tissue-engineering approach
2. Molecular biology of cartilage repair and its application to cartilage regenerative medicine
3. Development of novel scaffolds for cartilage and bone regeneration
4. In vivo evaluation of tissue-engineered cartilage and bone
5. Study on the control of mesenchymal cell differentiation
6. Elucidation of epigenetic abnormalities in oral cancers and oral premalignant lesions
7. Functional analysis of microRNAs in human dental pulp stem cells
8. Study on the cleft lip and osteonecrosis of the jaw using animal models
9. Elucidation of mechanisms of tissue repair by adipose-derived stem cells and macrophages
10. Analysis of regulatory mechanisms of bone using a reconstitution system of the cellular network in bone metabolism

Publication

(Original articles, Case report)

1. Kato H, Okawa R, Ogasawara T, Hoshino Y, Hidaka N, Koga M, Kinoshita Y, Kobayashi H, Taniguchi Y, Fukumoto S, Nangaku M, Makita N, Hoshi K, Nakano K, Ito N. Effect of Conventional Treatment on Dental Complications and Ectopic Ossifications Among 30 Adults With XLH. *J Clin Endocrinol Metab*. 2023 May 17;108(6):1405-1414. doi: 10.1210/clinem/dgac732. PMID: 36524341. [peer reviewed]
2. Itai S, Tonosaki K, Ono S, Watanabe R, Koshino S, Hoshi K, Yonenaga K. The inhibitory effect of catechin on the growth of oral bacteria in vitro and halitosis in a clinical setting. *Oral care*. 2023 Jun; 18(1) 27-32. [peer reviewed] .
3. Yonenaga K, Taga H, Yasumitsu T, Eno Y, Itai S, Takato T. Oral Palliative Care for Severe Side Effects of Nivolumab Administration Nivolumab. *Journal of Oral and Medical Science*. 2023 Aug; 1(1) 1-4. [peer reviewed]
4. Itai S, Yonenaga K, Ono S, Tonosaki K, Watanabe R, Hoshi K. Health effects of catechin in the daily intake of green tea. *Journal of Oral and Medical Science*. 2023 Sep; 1(2) 1-10. [peer reviewed]
5. Itai S, Tonosaki K, Ono S, Watanabe R, Hoshi K, Yonenaga K. Understanding the amount of dietary fluid that can be easily swallowed. *Journal of Oral and Medical Science*. 2023 Sep; 1(3) 1-3. [peer reviewed]
6. Uto S, Hikita A, Mori D, Sakamoto T, Yano F, Ohba S, Saito T, Takato T, Hoshi K. Subcutaneously Transplanted Fresh Cartilage in Allogeneic and Xenogeneic Immunocompetent Mouse. *Tissue Eng Part A*. 2023 Oct;29(19-20):541-556. doi: 10.1089/ten.TEA.2023.0052. PMID: 37548556
7. Shunsuke Itai, Natsuko Yoshimura Sawai, Yusuke Kozai, Takeharu Ikoma, Azuma Kosai, Mayumi Yakeishi, Nobuhisa Kubota, Takahiro Abe. Asymptomatic intraosseous leiomyoma in mandible: A case report and review of literature. *Journal of Oral and Maxillofacial Surgery, Medicine, and Pathology*. 2023 Nov; 35(6) 539-

544. doi: 10.1259/dmfr/22632903. PMID: 14709601. [peer reviewed]
 8. Inaki R, Sato Y, Nakamura D, Aikawa Y, Takato T, Hoshi K, Hikita A. Lipoaspirate stored at a constant low temperature by electric control suppresses intracellular metabolism and maintains high cell viability. *Regen Therapy*. 2023 Nov 21;24:662-669. doi: 10.1016/j.reth.2023.11.005
 9. Tonosaki K, Yonenaga K, Ono S, Itai S, Oyama S, Mizuno T, Watanabe Rinji W, Hoshi K. Saturation of Percutaneous Oxygen Decreases with Meal Consumption in Patients with Acute Pneumonia. *The Tokai Journal of Experimental and Clinical Medicine*. 2023 Dec; 48(4) 123-127. PMID:37981847. [peer reviewed]
 10. Zeng C, Hoshi K, Hikita A. miR-92a-3p-inspired shRNA exhibits pro-chondrogenic and chondrocyte protective effects in osteoarthritis treatment through targeting SMAD6/7. *J Bone Min Metab*. 2024 Jan;42:1-16. doi:10.1007/s00774-023-01474-3. Epub 2023 Dec 6. PMID: 38055109
 11. Hatori A, Fujii Y, Kawase-Koga Y, Ogasawara T, Chikira J, Minami S, Yamakawa D, Chikazu D. VCAM-1 and GFPT-2: Predictive markers of osteoblast differentiation in human dental pulp stem cells. *Bone*, 2023 Jan; 166:116575. doi: 10.1016/j.bone.2022.116575, Epub 2022 Oct 3, PMID: 36195245
 12. Abe M, Ohsato A, Fujihara Y, Hoshi K, Yanagimoto S. A comparative study of periodontal health status between international and domestic university students in Japan. *Int J Environ Res Public Health*, 2023 Feb 22; 20(5): 3866. doi: 10.3390/ijerph20053866, PMID: 36900877, PMCID:PMC10001467, **Free** PMC article
 13. Yoshizawa T, Kumagai K, Matsubara R, Nasu K, Kitaura K, Suzuki M, Hamada Y, Suzuki R. Characterization of metal-specific T-cells in inflamed oral mucosa in a novel murine model of chromium-induced allergic contact dermatitis. *Int J Mol Sci*, 2023 Feb 1; 24(3):2807. doi: 10.3390/ijms24032807 (Online)
 14. Nasu K, Kumagai K, Yoshizawa T, Kitaura K, Matsubara R, Suzuki M, Suzuki R, Hamada Y. Type IVb hypersensitivity reaction in the novel murine model of palladium-induced intraoral allergic contact mucositis. *Int J Mol Sci*, 2023 Feb 5; 24(4):3137. doi: 10.3390/ijms24043137. (Online)
 15. Matsubara R, Kumagai K, Nasu K, Yoshizawa T, Kitaura K, Suzuki M, Hamada Y, Suzuki R. Cross-reactivity of intraoral allergic contact mucositis in the nickel-sensitized ear model of metal allergy. *Int J Mol Sci*, 2023 Feb 16; 24(4):3965. doi: 10.3390/ijms24043965 (Online)
 16. Igarashi H, Nishizawa S, Miyamoto T, Hikita A, Hoshi K. Involvement of impaired angiogenesis and myelosuppression in antiresorptive-agent related osteonecrosis of the jaw mouse model. *Tokai J Exp Clin Med*, 2023 Apr 20; 48(1):22-31. PMID: 36999390
- (Review articles)
1. Fujii Y, Hatori A, Chikazu D, Ogasawara T. Application of dental pulp stem cells for bone and neural tissue regeneration in oral and maxillofacial region. *Stem Cells Int*, 2023 Mar 29; 2023:2026572. doi: 10.1155/2023/2026572, PMID: 37035445, PMCID: PMC10076122

Department of Orthopaedic Surgery

Professor

Sakae Tanaka, M.D., Ph.D.

Associate Professors

Taku Saito, M.D., Ph.D.

Yasushi Oshima, M.D., Ph.D.

Lecturers

Shuji Taketomi, M.D., Ph.D.

Takumi Matsumoto, M.D., Ph.D.

Hiroshi Kobayashi, M.D., Ph.D.

Specially Appointed Lecturer

Ryota Yamagami, M.D.

So Kato, M.D., Ph.D.

Associates

Hideki Nakamoto, M.D., Ph.D.

Kenta Makabe, M.D., Ph.D.

Ryutaro Takeda, M.D., Ph.D.

Junya Miyahara, M.D., Ph.D.

Sayaka Komine, M.D., Ph.D.

Takafumi Miyake, M.D.

Naoto Kaminaga, M.D., Ph.D.

Kazuhiro Kohata, M.D., Ph.D.

Koichi Okajima, M.D.

Takashi Kobayashi, M.D.

Masashi Sato, M.D.

Tatsuyuki Fukui, M.D.

Michita Noma, M.D.

Toshihiko Ando, M.D.

Homepage <http://www.u-tokyo-ortho.jp/>

Introduction and Organization

In 1906 our department was established as the first educational institute of orthopedic surgery in Japan, by the first professor Yoshinori Tashiro who had learned orthopedic surgery in Germany and Austria.

Initially, the department treated patients with infectious disorders and congenital malformations, such as poliomyelitis, tuberculosis of the spine, congenital clubfoot and hip dislocation. The number of outpatients visiting our department in 1910 was estimated to be no more than 3.3% of that of the two surgical departments in the University of Tokyo Hospital.

The number and characteristics of the patients, however, have changed dramatically in these 100 years. This is because our department addressed the acute needs of society from the beginning. Prof. Tashiro believed that trauma should be treated by orthopedists, so he provided his pupils with this training. Since 1950's, the department has increasingly been involved in the treatment of traffic and industrial accident victims. Prof. Tashiro and his successor professor Kenji Takagi devoted themselves to the establishment of an institute for children with disabilities. The arthroscopy was developed by Prof. Takagi, and is now considered to represent a breakthrough in the development of

minimally invasive surgery. We have recently been conducting many studies related to the ossification of spinal ligaments (OPLL), rheumatoid arthritis, biomechanics, and the degenerative skeletal disorders such as osteoporosis and osteoarthritis in response to the progressive aging of our society.

Our department is now adept in the entire field of medical science and medical practice related to the human locomotor system, the importance of which is now clearly recognized not only in Japan, but also all over the world. To meet the expanding needs of society, we have been conducting the teaching, clinical, and research activities described below.

Faculty members of the department are one professor, two associate professors, three lecturers, two specially appointed lecture, 14 associates, four medical staff members, and 12 senior residents.

Teaching activities

As for undergraduate education, our department provides a comprehensive series of lectures, physical assessment classes and problem-based learning (PBL) program to 4th year medical students, clinical clerkship programs to 5th year students and elective clinical clerkship programs to 6th year medical students.

A comprehensive series of lectures provides basic knowledge of the physiology, pathology, diagnosis and treatment of various musculoskeletal disorders. Twelve consecutive lectures in total cover a whole field of orthopaedics: basic science, pediatric disorders, rheumatic diseases, metabolic bone diseases, musculoskeletal neoplasm, trauma and regional disorders of the musculoskeletal system (spine, shoulder, elbow, hand, hip, knee, ankle and foot). In the physical assessment classes, we have provided physical diagnostic maneuvers and the radiological assessment of a variety of musculoskeletal diseases. PBL has been introduced to a small group of students to learn medical humanity and to develop a practical methodology to resolve clinical problems.

During the 3-week period of clinical clerkship program, students have opportunities to join one of clinical teams and experience patient care and orthopaedic practice with residents and faculty members. We have developed an original text for the students to learn on-site orthopedics effectively. They

are encouraged to participate in clinical conferences and surgeries. They are also required to submit reports on the cases they are involved in. They learn how to conduct a medical interview, check physical findings and draw up actual plans for a diagnosis and treatment including surgery.

Elective clinical clerkship provides 4 weeks of more intensive exposure to the clinical practice. The students are attached to a clinical team and are involved in most of the clinical activities performed by the team.

For postgraduate education, junior residents join our department for 1-8 months. In 12 doctors-in-training completed our program during this fiscal year. Since the training period is short, they are encouraged to experience emergency cases as often as possible to learn primary care. For senior residents, 1-year clinical programs were conducted in corporation with our affiliated hospitals. A postgraduate seminar and a basic research conference are held weekly.

Including the postgraduate training, an eight-year course has been adopted with clinical and research training taking place either in the University of Tokyo Hospital or in our 40 affiliated hospitals.

Clinical activities

We have the outpatient clinic open from Monday through Friday, with specialized divisions for spine, hip, rheumatoid arthritis, tumor, scoliosis, limb reconstruction and bone lengthening, knee, hand, elbow, shoulder, sports, peripheral nerves, bone systemic disorders, and foot. A total of 33,952 patients visited the outpatient clinic in fiscal 2023.

The ward has approximately 60 to 70 beds available and is divided into the subgroups above. The members are on duty for daily patient care under the supervision of faculty members. The weekly official activities of our department include ward rounds by the professor on Thursday. Post- and preoperative case conferences are held on Monday evening, Wednesday evening and Thursday morning.

1,434 operations were performed in fiscal 2023. These include 336 spine surgeries, 56 surgeries for rheumatoid arthritis patients, 130 hip surgeries, 270 knee surgeries, 235 hand surgeries, 41 foot and ankle surgeries, 28 pediatric surgeries, 172 surgeries for bone and soft tissue tumor, and 148 trauma surgeries.

The main disorders of cervical spine surgery were myelopathy due to spondylosis or OPLL. We successfully adopted double-door open laminoplasty by splitting the spinal processes for most of these cases. This procedure was invented and developed in our department and is now used nationwide. Difficult operations such as subluxation of the cervical spine due to rheumatoid arthritis, Down's syndrome or cerebral palsy were treated using a navigation system that has been officially approved as a high-level advanced medical treatment.

The spine group is now converting open surgeries to minimum invasive surgeries using endoscopic technique. In 2012, the cervical microendoscopic Interlaminar decompression through a midline approach (CMID) was developed, and has been yielding favorable results in selected patients with cervical myelopathy.

The scoliosis group used the navigation system especially for patients with complex deformity. In addition to the conventional correction surgery, growth-assist techniques such as dual growing rods are utilized.

Main operations performed by the rheumatoid arthritis clinic group were total joint arthroplasty. They are using image-free navigation system in total knee arthroplasty operation, which is useful for the accurate placement of the implants.

The hip surgery group treated mainly acetabular dysplasia and osteoarthritis of the hip joint. They performed not only total hip replacements, but also several osteotomies including rotational acetabular osteotomy (RAO). The RAO was originated and established in our department. They conducted a clinical trial for a new artificial hip joint using the MPC polymer in collaboration with the Department of Materials Engineering in Tokyo University.

The knee clinic group developed a new anterior cruciate ligament reconstruction technique using the navigation system based on intraoperative three-dimensional fluoroscopic image to realize ideal graft placement.

The peripheral nerve clinic group has developed "costal nerve transfer to the musculocutaneous nerve" for brachial plexus injury.

The tumor group managed multidisciplinary treatment for musculoskeletal sarcoma including chemo-

therapy, limb sparing surgery and radiotherapy in cooperation with other departments.

Limb reconstruction operations using external fixators included non-union, leg lengthening and deformity correction. One of the main interests of this group is the development of a system to analyze the mechanical properties of a skeletal system. During this period of analysis, the mechanical properties of the fracture site in vivo are to be evaluated by monitoring the motion of a dynamic pin clamp during simulated walking.

Research activities

Our research activities cover the full range of the musculoskeletal system medicine, using the in-depth sciences of biology and technology. Especially in the field of molecular biology of bone and cartilage metabolism, we are regarded as being on the leading edge in the world. Basic research is performed under the supervision of the faculty staff members. Five endowment departments take an active role in research activities in close collaboration with our department. They deal with regenerative medicine, clinical research, and material engineering.

As for research of bone resorption, we have been researching and released some important reports about bone metabolism, especially in differentiation, activation and apoptosis of osteoclast. Recently we have been getting achievement in the new research topics such as "Osteoimmunology", a new research field studying on signaling cross-talk between bone metabolism and immunology, or "Epigenetics", new research concept in spotlight using comprehensive analysis technique.

As for research of cartilage, we have researched molecular biology of cartilage with the students of the graduate school and the members of Bone and Cartilage Regenerative Medicine. Our research activities cover the generation and differentiation of chondrocytes, the joint formation, the degeneration of joint cartilage, and the regenerative methods.

Our clinical groups also take part in many multicenter clinical studies conducted by Japan Musculoskeletal Oncology Group (JMOG), National Database of Rheumatic Diseases by iR-net in Japan (NinJa), and other multicenter groups. In 2017, the

NPO Tokyo University Spine Group was established, proactively registering all spine surgeries at affiliated facilities and sharing surgical outcomes. As of August 2023, 32,440 spine surgeries have been registered.

Publications

- 1: Tani S, Okada H, Onodera S, Chijimatsu R, Seki M, Suzuki Y, Xin X, Rowe DW, Saito T, Tanaka S, Chung UI, Ohba S, Hojo H. Stem cell-based modeling and single-cell multiomics reveal gene-regulatory mechanisms underlying human skeletal development. *Cell Rep.* 2023 Apr 25;42(4):112276. doi:10.1016/j.celrep.2023.112276. Epub 2023 Mar 24. PMID: 36965484.
- 2: Oichi T, Kodama J, Wilson K, Tian H, Imamura Kawasawa Y, Usami Y, Oshima Y, Saito T, Tanaka S, Iwamoto M, Otsuru S, Enomoto-Iwamoto M. Nutrient-regulated dynamics of chondroprogenitors in the postnatal murine growth plate. *Bone Res.* 2023 Apr 21;11(1):20. doi: 10.1038/s41413-023-00258-9. PMID: 37080994; PMCID: PMC10119120.
- 3: Murase S, Sakitani N, Maekawa T, Yoshino D, Takano K, Konno A, Hirai H, Saito T, Tanaka S, Shinohara K, Kishi T, Yoshikawa Y, Sakai T, Ayaori M, Inanami H, Tomiyasu K, Takashima A, Ogata T, Tsuchimochi H, Sato S, Saito S, Yoshino K, Matsuura Y, Funamoto K, Ochi H, Shinohara M, Nagao M, Sawada Y. Interstitial- fluid shear stresses induced by vertically oscillating head motion lower blood pressure in hypertensive rats and humans. *Nat Biomed Eng.* 2023 Nov;7(11):1350-1373. doi: 10.1038/s41551-023-01061-x. Epub 2023 Jul 6. Erratum in: *Nat Biomed Eng.* 2023 Nov;7(11):1530. doi: 10.1038/s41551-023-01152-9. PMID: 37414976; PMCID: PMC10651490.
- 4: Murakami R, Taketomi S, Yamagami R, Kono K, Kawaguchi K, Kage T, Arakawa T, Inui H, Tanaka S. Postoperative quadriceps weakness and male sex are risk factors for patellofemoral articular cartilage lesions after anatomical anterior cruciate ligament reconstruction. *Knee Surg Sports Traumatol Arthrosc.* 2023 Dec;31(12):5681-5689. doi: 10.1007/s00167-023-07633-3. Epub 2023 Oct 26. PMID: 37884728; PMCID: PMC10719126.
- 5: Kobayashi H, Zhang L, Okajima K, Ishibashi Y, Hirai T, Tsuda Y, Ikegami M, Kage H, Shinozaki-Ushiku A, Oda K, Tanaka S. BRAF mutations and concurrent alterations in patients with soft tissue sarcoma. *Genes Chromosomes Cancer.* 2023 Nov; 62(11):648-654. doi: 10.1002/gcc.23182. Epub 2023 Jun 9. PMID: 37293958.
- 6: Inui H, Yamagami R, Kono K, Kawaguchi K, Kage T, Murakami R, Nakamura H, Saita K, Taketomi S, Tanaka S. Short-term clinical results of bicruciate- retaining total knee arthroplasty using personalized alignment. *BMC Musculoskelet Disord.* 2023 Dec 12; 24(1): 965. doi: 10.1186/s12891-023-07083-5. PMID: 38087214; PMCID: PMC10714564.
- 7: Sasaki K, Doi T, Inoue T, Tozawa K, Nakarai H, Yoshida Y, Ito Y, Ohtomo N, Sakamoto R, Nakajima K, Nagata K, Okamoto N, Nakamoto H, Kato S, Taniguchi Y, Matsubayashi Y, Okazaki K, Tanaka S, Oshima Y. Bone Turnover Markers in Patients With Ossification of the Posterior Longitudinal Ligament in the Thoracic Spine. *Spine (Phila Pa 1976).* 2024 Apr 15;49(8):E100-E106. doi: 10.1097/BRS.0000000000004753. Epub 2023 Jun 19. PMID: 37339262.
- 8: Murase S, Sakitani N, Maekawa T, Yoshino D, Takano K, Konno A, Hirai H, Saito T, Tanaka S, Shinohara K, Kishi T, Yoshikawa Y, Sakai T, Ayaori M, Inanami H, Tomiyasu K, Takashima A, Ogata T, Tsuchimochi H, Sato S, Saito S, Yoshino K, Matsuura Y, Funamoto K, Ochi H, Shinohara M, Nagao M, Sawada Y. Author Correction: Interstitial-fluid shear stresses induced by vertically oscillating head motion lower blood pressure in hypertensive rats and humans. *Nat Biomed Eng.* 2023 Nov;7(11):1530. doi: 10.1038/s41551-023-01152-9. Erratum for: *Nat Biomed Eng.* 2023 Nov;7(11):1350-1373. doi: 10.1038/s41551-023-01061-x. PMID: 37935932; PMCID: PMC10651474.
- 9: Mizutani Y, Taketomi S, Kawaguchi K, Takei S, Yamagami R, Kono K, Kage T, Sameshima S, Inui H, Fujiwara S, Tanaka S, Ogata T. Risk factors for hamstring strain injury in male college American football players -a preliminary prospective cohort study. *BMC Musculoskelet Disord.* 2023 Jun 2;

- 24(1):448. doi: 10.1186/s12891-023-06565-w. PMID: 37269013; PMCID: PMC10236836.
- 10: Hidaka R, Tanaka T, Hashikura K, Oka H, Matsudaira K, Moro T, Matsuda K, Kawano H, Tanaka S. Association of high kinesiphobia and pain catastrophizing with quality of life in severe hip osteoarthritis: a cross-sectional study. *BMC Musculoskelet Disord*. 2023 May 16;24(1):388. doi: 10.1186/s12891-023-06496-6. PMID: 37194069; PMCID: PMC10186760.
- 11: Oshima Y, Ohtomo N, Kawamura N, Higashikawa A, Hara N, Ono T, Takeshita Y, Fukushima M, Azuma S, Kato S, Matsubayashi Y, Taniguchi Y, Tanaka S. Impact of the COVID-19 pandemic on surgical volume and outcomes in spine surgery: a multicentre retrospective study in Tokyo. *BMJ Open*. 2023 Nov 29;13(11):e077110. doi: 10.1136/bmjopen-2023-077110. PMID: 38030245; PMCID: PMC10689418.
- 12: Asano S, Ogawa A, Osada T, Oka S, Nakajima K, Oshima Y, Tanaka S, Kaga H, Tamura Y, Watada H, Kawamori R, Konishi S. Reduced gray matter volume in the default-mode network associated with insulin resistance. *Cereb Cortex*. 2023 Nov 27;33(23):11225-11234. doi: 10.1093/cercor/bhad358. PMID: 37757477.
- 13: Inoue I, Yoshimura N, Iidaka T, Horii C, Muraki S, Oka H, Kawaguchi H, Akune T, Maekita T, Mure K, Nakamura K, Tanaka S, Ichinose M. Trends in the prevalence of atrophic gastritis and *Helicobacter pylori* infection over a 10-year period in Japan: The ROAD study 2005-2015. *Mol Clin Oncol*. 2023 May 19;19(1):53. doi: 10.3892/mco.2023.2649. PMID: 37323249; PMCID: PMC10265571.
- 14: Takei S, Torii S, Taketomi S, Iizuka S, Tojima M, Iwanuma S, Iida Y, Tanaka S. Developmental stage and lower quadriceps flexibilities and decreased gastrocnemius flexibilities are predictive risk factors for developing Osgood-Schlatter disease in adolescent male soccer players. *Knee Surg Sports Traumatol Arthrosc*. 2023 Aug;31(8):3330-3338. doi: 10.1007/s00167-023-07378-z. Epub 2023 Mar 31. PMID: 37002485; PMCID: PMC10356628.
- 15: Nakajima K, Miyahara J, Ohtomo N, Nagata K, Kato S, Doi T, Matsubayashi Y, Taniguchi Y, Kawamura N, Higashikawa A, Takeshita Y, Fukushima M, Ono T, Hara N, Azuma S, Iwai H, Oshima M, Sugita S, Hirai S, Masuda K, Tanaka S, Oshima Y. Impact of body mass index on outcomes after lumbar spine surgery. *Sci Rep*. 2023 May 15;13(1):7862. doi: 10.1038/s41598-023-35008-8. PMID: 37188788; PMCID: PMC10185565.
- 16: Oshima Y, Kato S, Doi T, Taniguchi Y, Matsubayashi Y, Ohtomo N, Watanabe K, Kyomoto M, Tanaka S, Moro T. A dynamic pedicle screw system using polyethylene insert for the lumbar spine. *J Biomed Mater Res B Appl Biomater*. 2023 Apr;111(4):805-811. doi: 10.1002/jbm.b.35191. Epub 2022 Nov 18. PMID: 36401346.
- 17: Oichi T, Kodama J, Wilson K, Tian H, Imamura Y, Usami Y, Oshima Y, Saito T, Tanaka S, Iwamoto M, Otsuru S, Iwamoto-Enomoto M. Nutrient-regulated dynamics of chondroprogenitors in the postnatal murine growth plate. *bioRxiv [Preprint]*. 2023 Jan 20:2023.01.20.524764. doi: 10.1101/2023.01.20.524764. Update in: *Bone Res*. 2023 Apr 21;11(1):20. doi: 10.1038/s41413-023-00258-9. PMID: 36711544; PMCID: PMC9882259.
- 18: Matsumoto T, Takeda R, Uchio A, Mizuhara H, Omata Y, Juji T, Tanaka S. Associated correction of forefoot alignment with hindfoot fusion for pes planovalgus deformity. *Foot Ankle Surg*. 2023 Apr;29(3):280-287. doi: 10.1016/j.fas.2023.02.012. Epub 2023 Feb 28. PMID: 36870925.
- 19: Taniguchi Y, Akune T, Nishida N, Omori G, Ha K, Ueno K, Saito T, Oichi T, Koike A, Mabuchi A, Oka H, Muraki S, Oshima Y, Kawaguchi H, Nakamura K, Tokunaga K, Tanaka S, Yoshimura N. A common variant rs2054564 in ADAMST17 is associated with susceptibility to lumbar spondylosis. *Sci Rep*. 2023 Mar 25;13(1):4900. doi: 10.1038/s41598-023-32155-w. PMID: 36966180; PMCID: PMC10039864.
- 20: Ito Y, Doi T, Ohtomo N, Fujii Y, Ono K, Kojima E, Yamada T, Tran HH, Goffinet F, Endo Y, Kato S, Matsubayashi Y, Tanaka S, Oshima Y, Taniguchi Y. A Novel Screening Method for Scoliosis Using a Bodysuit and 3-Dimensional Imaging. *Spine (Phila Pa 1976)*. 2023 Sep 15;48(18):1289-1294.

- doi: 10.1097/BRS.0000000000004658. Epub 2023 Jun 29. PMID: 37389986.
- 21: Kobayashi H, Ito N, Nakai Y, Katoh H, Okajima K, Zhang L, Tsuda Y, Tanaka S. Patterns of symptoms and insufficiency fractures in patients with tumour-induced osteomalacia. *Bone Joint J.* 2023 May 1;105-B(5):568-574. doi: 10.1302/0301-620X.105B5.BJJ-2022-1206.R2. PMID: 37121579.
 - 22: Nagata K, Hashizume H, Oka H, Ishimoto Y, Muraki S, Nakamura K, Yoshida M, Tanaka S, Yamada H, Yoshimura N. Plasma pentosidine concentration is associated with ligament ossification and high-grade osteoarthritis: The ROAD study. *Geriatr Gerontol Int.* 2024 Jan; 24(1):154-160. doi: 10.1111/ggi.14745. Epub 2023 Nov 29. PMID: 38031320.
 - 23: Murata S, Hashizume H, Tsutsui S, Oka H, Teraguchi M, Ishimoto Y, Nagata K, Takami M, Iwasaki H, Minamide A, Nakagawa Y, Tanaka S, Yoshimura N, Yoshida M, Yamada H. Pelvic compensation accompanying spinal malalignment and back pain- related factors in a general population: the Wakayama spine study. *Sci Rep.* 2023 Jul 22;13(1):11862. doi: 10.1038/s41598-023-39044-2. Erratum in: *Sci Rep.* 2023 Aug 7;13(1):12791. doi: 10.1038/s41598-023-39895-9. PMID: 37481604; PMCID: PMC10363166.
 - 24: Onodera R, Sakamoto R, Taniguchi Y, Hirai S, Matsubayashi Y, Kato S, Oshima Y, Tanaka S. Congenital atlanto-occipital dislocation in a patient with Down syndrome: a case report. *Skeletal Radiol.* 2023 Sep;52(9):1785-1789. doi: 10.1007/s00256-023-04297-5. Epub 2023 Feb 11. PMID: 36773086; PMCID: PMC10348997.
 - 25: Higuchi J, Matsumoto T, Kasai T, Takeda R, Iidaka T, Horii C, Oka H, Muraki S, Hashizume H, Yamada H, Yoshida M, Nakamura K, Tanaka S, Yoshimura N. Relationship between medial partite hallux sesamoid and hallux valgus in the general population. *Foot Ankle Surg.* 2023 Dec;29(8): 621-626. doi: 10.1016/j.fas.2023.07.011. Epub 2023 Jul 25. PMID: 37679197.
 - 26: Kato S, Miyahara J, Matsubayashi Y, Taniguchi Y, Doi T, Kodama H, Higashikawa A, Takeshita Y, Fukushima M, Ono T, Hara N, Azuma S, Iwai H, Oshima M, Sugita S, Hirai S, Masuda K, Tanaka S, Oshima Y; University of Tokyo Spine Group. Predictors for hemostatic thrombin-gelatin matrix usage in spine surgery: a multicenter observational study. *BMC Musculoskelet Disord.* 2023 Apr 13;24(1):289. doi: 10.1186/s12891-023-06408-8. PMID: 37055735; PMCID: PMC10099820.
 - 27: Kono K, Konda S, Yamazaki T, Taketomi S, Yamagami R, Kawaguchi K, Kage T, Arakawa T, Inui H, Tanaka S, Tomita T. Comparison of finite helical axis of the knee joint before and after bi-cruciate-preserving knee arthroplasty. *Clin Biomech (Bristol).* 2023 Oct;109:106098. doi: 10.1016/j.clinbiomech.2023.106098. Epub 2023 Sep 17. PMID: 37729737.
 - 28: Yamato Y, Nagata K, Kawamura N, Higashikawa A, Takeshita Y, Tozawa K, Fukushima M, Urayama D, Ono T, Hara N, Okamoto N, Azuma S, Iwai H, Sugita S, Yoshida Y, Hirai S, Masuda K, Jim Y, Ohtomo N, Nakamoto H, Kato S, Taniguchi Y, Tanaka S, Oshima Y. Comparative Analysis of Microendoscopic and Open Laminectomy for Single-Level Lumbar Spinal Stenosis at L1-L2 or L2-L3. *World Neurosurg.* 2024 Mar;183:e408-e414. doi: 10.1016/j.wneu.2023.12.109. Epub 2023 Dec 23. PMID: 38143029.
 - 29: Yoshida Y, Doi T, Oka H, Kato S, Ohtomo N, Nakamoto H, Takeda N, Inuzuka R, Yagi H, Oshima Y, Tanaka S, Fukatsu K, Taniguchi Y. Reduced volume and altered composition of paraspinal muscles in Marfan syndrome: A retrospective cohort study. *Medicine (Baltimore).* 2023 Sep 29;102(39):e35382. doi: 10.1097/MD.00000000000035382. PMID: 37773813; PMCID: PMC10545292.
 - 30: Nagata K, Miyahara J, Tozawa K, Ito Y, Schmidt G, Chang C, Sasaki K, Yamato Y, Ohtomo N, Nakajima K, Kato S, Doi T, Taniguchi Y, Matsubayashi Y, Sumitani M, Tanaka S, Oshima Y. Adaptation and Limitations of painDETECT Questionnaire Score Approach Before and After Posterior Cervical Decompression Surgery. *World Neurosurg.* 2023 Aug;176:e391-e399. doi: 10.1016/j.wneu.2023.05.072. Epub 2023 May 24. PMID: 37236307.
 - 31: Kage T, Taketomi S, Tomita T, Yamazaki T, Inui H, Yamagami R, Kono K, Kawaguchi K, Sameshima S, Arakawa T, Tanaka S. Anterior cruciate

- ligament- deficient knee induces a posterior location of the femur in the medial compartment during squatting. *J Orthop Res.* 2023 Jul;41(7):1439-1448. doi: 10.1002/jor.25501. Epub 2022 Dec 20. PMID: 36484121.
- 32: Murata S, Hashizume H, Tsutsui S, Oka H, Teraguchi M, Ishimoto Y, Nagata K, Takami M, Iwasaki H, Minamide A, Nakagawa Y, Tanaka S, Yoshimura N, Yoshida M, Yamada H. Publisher Correction: Pelvic compensation accompanying spinal malalignment and back pain-related factors in a general population: the Wakayama spine study. *Sci Rep.* 2023 Aug 7;13(1):12791. doi: 10.1038/s41598-023-39895-9. Erratum for: *Sci Rep.* 2023 Jul 22;13(1):11862. doi: 10.1038/s41598-023-39044-2. PMID: 37550444; PMCID: PMC10406805.
 - 33: Nakajima K, Miyata A, Kato S, Oshima Y, Tanaka S. Calcific tendinitis of the shoulder induced by an mRNA vaccine for COVID-19: A case report. *Mod Rheumatol Case Rep.* 2023 Jan 3;7(1):211-214. doi: 10.1093/mrcr/rxac006. PMID: 35134200; PMCID: PMC8903335.
 - 34: Teraguchi M, Hashizume H, Oka H, Kagotani R, Nagata K, Ishimoto Y, Tanaka S, Yoshida M, Yoshimura N, Yamada H. Prevalence and distribution of Schmorl node and endplate signal change, and correlation with disc degeneration in a population-based cohort: the Wakayama Spine Study. *Eur Spine J.* 2024 Jan;33(1):103-110. doi: 10.1007/s00586-023-08009-4. Epub 2023 Oct 31. PMID: 37907767.
 - 35: Tachibana N, Doi T, Nakajima K, Nakamoto H, Miyahara J, Nagata K, Nakarai H, Tozawa K, Ohtomo N, Sakamoto R, Kato S, Taniguchi Y, Matsubayashi Y, Tanaka S, Oshima Y. Does Surgical Treatment Affect the Degree of Anxiety or Depression in Patients With Degenerative Cervical Myelopathy? *Global Spine J.* 2023 Oct;13(8):2479-2487. doi:10.1177/21925682221088549. Epub 2022 Mar 29. PMID: 35349781; PMCID: PMC10538321.
 - 36: Nakarai H, Kato S, Yamato Y, Kodama H, Ohba Y, Sasaki K, Iizuka T, Tozawa K, Urayama D, Komatsu N, Okazaki R, Oshima M, Ogiso S, Masuda K, Maayan O, Tanaka S, Oshima Y. Quality of Life and Postoperative Satisfaction in Patients with Benign Extramedullary Spinal Tumors: A Multicenter Study. *Spine (Phila Pa 1976).* 2023 Sep 15;48(18):E308-E316. doi: 10.1097/BRS.0000000000004771. Epub 2023 Jul 6. PMID: 37417695.
 - 37: Ogata T, Yamada K, Miura H, Hino K, Kutsuna T, Watamori K, Kinoshita T, Ishibashi Y, Yamamoto Y, Sasaki T, Matsuda S, Kuriyama S, Watanabe M, Tomita T, Tamaki M, Ishibashi T, Okazaki K, Mizu-Uchi H, Ishibashi S, Ma Y, Ito YM, Nakamura K, Tanaka S. Feasibility and applicability of locomotive syndrome risk test in elderly patients who underwent total knee arthroplasty. *Mod Rheumatol.* 2023 Nov 1;33(6):1197-1203. doi: 10.1093/mr/roac131. PMID: 36318460.
 - 38: Kobayashi H, Makise N, Shinozaki-Ushiku A, Zhang L, Ishibashi Y, Ikegami M, Tsuda Y, Kohsaka S, Ushiku T, Oda K, Miyagawa K, Aburatani H, Mano H, Tanaka S. Dramatic response to entrectinib in a patient with malignant peripheral nerve sheath tumor harboring novel SNRNP70-NTRK3 fusion gene. *Genes Chromosomes Cancer.* 2023 Jan;62(1):47-51. doi: 10.1002/gcc.23089. Epub 2022 Aug 18. PMID: 35906852.
 - 39: Taniguchi Y, Takeda N, Inuzuka R, Matsubayashi Y, Kato S, Doi T, Yagi H, Yamauchi H, Ando M, Oshima Y, Tanaka S. Impact of pathogenic *FBN1* variant types on the development of severe scoliosis in patients with Marfan syndrome. *J Med Genet.* 2023 Jan;60(1):74-80. doi: 10.1136/jmedgenet-2021-108186. Epub 2021 Dec 16. PMID: 34916231; PMCID: PMC9811093.
 - 40: Tozawa K, Nagata K, Ohtomo N, Ito Y, Nakamoto H, Kato S, Doi T, Taniguchi Y, Matsubayashi Y, Tanaka S, Oshima Y. Effect of Early Postoperative Resolution of MRI Signal Intensity Changes on the Outcomes of Degenerative Cervical Myelopathy. *Spine (Phila Pa 1976).* 2023 May 1;48(9):591-599. doi: 10.1097/BRS.0000000000004612. Epub 2023 Feb 27. PMID: 36856449.
 - 41: Yamagami R, Inui H, Taketomi S, Kono K, Kawaguchi K, Sameshima S, Kage T, Arakawa T, Tanaka S. Intraoperative femoral rotational kinematics are similar in varus and valgus knees during medial pivot total knee arthroplasty. *Clin*

- Biomech (Bristol). 2023 Jan;101:105857. doi: 10.1016/j.clinbiomech.2022.105857. Epub 2022 Dec 9. PMID: 36521411.
- 42: Miyake T, Uehara K, Kohata K, Miura T, Ohe T, Tanaka S, Morizaki Y. New body surface indexes for germinal matrix: DIP joint extension boundary line and dorsal distal interphalangeal crease. *J Orthop Sci.* 2023 Sep;28(5):1023-1026. doi: 10.1016/j.jos.2022.07.017. Epub 2022 Sep 15. PMID: 36117033.
 - 43: Takeda R, Matsumoto T, Omata Y, Inui H, Taketomi S, Nagase Y, Nishikawa T, Oka H, Tanaka S. Changes in knee joint destruction patterns among patients with rheumatoid arthritis undergoing total knee arthroplasty in recent decades. *Clin Rheumatol.* 2023 Sep;42(9):2341-2352. doi: 10.1007/s10067-023-06620-w. Epub 2023 May 24. PMID: 37222908; PMCID: PMC10412667.
 - 44: Kobayashi H, Zhang L, Okajima K, Hirai T, Tsuda Y, Ikegami M, Kawai A, Tanaka S. Role of perioperative chemotherapy and radiotherapy for localized high-grade malignant peripheral nerve sheath tumor at the extremities and trunk wall: a population-based cohort study. *Jpn J Clin Oncol.* 2023 Jan 28;53(2):138-145. doi: 10.1093/jjco/hyac178. PMID: 36461784.
 - 45: Doi T, Horii C, Tozawa K, Nakarai H, Sasaki K, Yoshida Y, Ito Y, Ohtomo N, Sakamoto R, Nakajima K, Nagata K, Okamoto N, Nakamoto H, Kato S, Taniguchi Y, Matsubayashi Y, Tanaka S, Oshima Y. Noninvasive Skin Autofluorescence of Advanced Glycation End Products for Detecting Ossification of the Posterior Longitudinal Ligament in the Thoracic Spine. *Spine (Phila Pa 1976).* 2023 Feb 15;48(4):E40-E45. doi: 10.1097/BRS.0000000000004516. Epub 2022 Nov 4. PMID: 36692158.
 - 46: Doi T, Ohtomo N, Oguchi F, Tozawa K, Nakarai H, Nakajima K, Sakamoto R, Okamoto N, Nakamoto H, Kato S, Taniguchi Y, Matsubayashi Y, Oka H, Matsudaira K, Tanaka S, Oshima Y. Association Between Deep Posterior Cervical Paraspinal Muscle Morphology and Clinical Features in Patients With Cervical Ossification of the Posterior Longitudinal Ligament. *Global Spine J.* 2023 Jan;13(1):8-16. doi: 10.1177/2192568221989655. Epub 2021 Jan 28. PMID: 33504203; PMCID: PMC9837499.
 - 47: Takagi K, Taketomi S, Yamagami R, Kawaguchi K, Sameshima S, Kage T, Tanaka S, Inui H. Both Intraoperative Medial and Lateral Joint Stabilities at Midflexion Influence Postoperative Patient-Reported Outcome Measures Following Bi-Cruciate Stabilized Total Knee Arthroplasty. *J Knee Surg.* 2023 Jul;36(8):857-865. doi: 10.1055/s-0042-1744191. Epub 2022 Mar 8. PMID: 35259765.
 - 48: Teraguchi M, Hashizume H, Asai Y, Oka H, Nagata K, Ishimoto Y, Iwasaki H, Tsutsui S, Takami M, Tanaka S, Yoshida M, Yoshimura N, Yamada H. Association between modic changes, disc degeneration, and pelvic incidence-lumbar lordosis mismatch in a large population based cohort: the Wakayama spine study. *Eur Spine J.* 2023 Apr 26. doi: 10.1007/s00586-023-07702-8. Epub ahead of print. PMID: 37100965.
 - 49: Kono K, Inui H, Tomita T, Yamazaki T, Konda S, Taketomi S, Tanaka S, D'Lima DD. Bicruciate-retaining total knee arthroplasty procedure reduced tensile force in the middle and posterior components of lateral collateral ligament during deep knee flexion activities with no effect on tensile force of the medial collateral ligament. *Knee Surg Sports Traumatol Arthrosc.* 2023 Sep;31(9):3889-3897. doi: 10.1007/s00167-023-07342-x. Epub 2023 Mar 16. PMID: 36928366.
 - 50: Nakamoto H, Nakajima K, Miyahara J, Kato S, Doi T, Taniguchi Y, Matsubayashi Y, Nishizawa M, Kawamura N, Kumanomido Y, Higashikawa A, Sasaki K, Takeshita Y, Fukushima M, Iizuka M, Ono T, Yu J, Hara N, Okamoto N, Azuma S, Inanami H, Sakamoto R, Tanaka S, Oshima Y. Does surgical site infection affect patient-reported outcomes after spinal surgery? A multicenter cohort study. *J Orthop Sci.* 2024 Nov;29(6):1370-1375. doi: 10.1016/j.jos.2023.10.010. Epub 2023 Oct 28. PMID: 37903677.
 - 51: Taketomi S, Kawaguchi K, Mizutani Y, Takei S, Yamagami R, Kono K, Murakami R, Kage T, Arakawa T, Fujiwara S, Tanaka S, Ogata T. Lower hamstring to quadriceps muscle strength ratio and lower body weight as factors associated with noncontact anterior cruciate ligament injury in

male American football players: A prospective cohort study. *Asia Pac J Sports Med Arthrosc Rehabil Technol.* 2023 Dec 15;35:43-47. doi: 10.1016/j.asmart.2023.11.006. PMID: 38187929; PMCID: PMC10770439.

Department of Ophthalmology

Professor

Makoto Aihara, M.D., Ph.D.

Associate Professor

Megumi Honjo, M.D., Ph.D., Ryo Obata, M.D., Ph.D., Takashi Miyai, M.D., Ph.D.

Lecturer

Hitomi Saito, M.D., Ph.D., Hiromasa Sawamura, M.D., Ph.D., Rei Sakata, M.D., Ph.D.,
Rie Tanaka, M.D., Ph.D.

Research Associate

Takashi Ueta, M.D., Ph.D., Keiko Azuma, M.D., Ph.D., Tetsuya Toyono, M.D., Ph.D.,
Taku Toyama, M.D., Ph.D., Yukako Taketani, M.D., Ph.D., Sugimoto Koichiro, M.D.,
Ishiyama Yukako, M.D., Kohdai Kitamoto, M.D., Ph.D., Arai Takahiro, M.D.,
Ono Takashi, M.D., Ph.D., Aoki Shuichiro, M.D., Aoyama Yurika, M.D., Shu Kanhou, M.D.

※The following information is the same as that of the previous year for certain reasons.

Homepage <https://www.todaiganka.jp>

Introduction and Organization

The Department of Ophthalmology, University of Tokyo School of Medicine, was founded in 1889. Since then, the department has contributed to Japanese ophthalmology not only by educating many eminent ophthalmologists in Japan but also by producing significant basic research in ophthalmology.

The department has been active in collaboration with ophthalmologists around the world, sponsoring international ophthalmological meetings, educating fellows from foreign countries, and sending our staff and fellows abroad.

Clinical activities

Altogether, approximately 2900 new outpatients are seen every year in our hospital, which has a total of 27 beds. Residents work in the ambulatory section and take care of inpatients. Special services are provided in units devoted to ophthalmic subspecialties such as

cornea, glaucoma, retina, uveitis, neuro-ophthalmology, orthoptics, diabetic retinopathy, and genetic and color blindness problems. The staff members supervise the ambulatory and special services depending on each one's specialty.

Most of the inpatients suffer from cataract, glaucoma, corneal diseases, retinal detachment, diabetic retinopathy, age-related macular degeneration, uveitis, ptosis, dry eye and strabismus. Surgeries are performed in the operating theater of the hospital under operating microscopes. Approximately 8610 cases underwent operations in our department. Surgeries can be monitored by TV system, which is mounted on operating microscopes. Since multiple observers can watch the same images and share findings, this system has great potential in training and promoting discussion.

Education

As an undergraduate course, we give lectures on

corneal physiology, corneal diseases, and corneal transplantation. In addition, we are engaged in practical training for medical students on ophthalmological examinations at the outpatient clinic. As a postgraduate course, we give lectures on topics concerning corneal transplantation, corneal diseases and new medical therapies.

Research

Research topics in our department cover a variety of fields in ophthalmology; e.g. ocular pharmacology in glaucoma, lipid mediators in ocular diseases, regenerative medicine in the cornea and retina, aqueous humor dynamics, immunology and molecular biology. Special laboratories for physiology, pharmacology and genetic engineering have been established. Specific fields of research in our department are as follows.

1. Lipid mediators in ocular diseases
2. Clinical investigation of normal tension glaucoma
3. Drug development in IOP reduction of glaucoma
4. Screening method of glaucoma
5. Pathophysiology and molecular mechanisms of diabetic retinopathy
6. Relationship between visual function and quality of life in patient with low vision
7. Investigation of molecular mechanisms of retinal arteritis and phlebitis
8. Investigation of gene mutations in primary vitreoretinal lymphoma and development of new treatment
9. Study of mechanisms involving disease-specific HLA in Behcet's disease
10. Analysis of structure-function relationships in macular diseases
11. Molecular analysis of corneal neovascularization
12. Gene therapy for corneal dystrophies
13. Analysis of Meibomian gland with Mibography
14. Analysis of safety of topical eye drops using human corneal epithelial cell sheets
15. Clinical trial of corneal crosslinking for keratoconus and keratoectasia
16. Ophthalmic examination of patients with congenital insensitivity to pain with anhydrosis
17. Assessment of higher visual functions by fMRI
18. Relevance between ophthalmic diseases and cortical functions

Publications

1. Liu Y, Yamagishi R, Honjo M, Kurano M, Yatomi Y, Igarashi K, Aihara M. Role of Autotaxin in High Glucose-Induced Human ARPE-19 Cells. *Int J Mol Sci.* 2022 Aug 16; 23(16):9181.
2. Fujishiro T, Honjo M, Kawasaki H, Aihara M. Visual cortex damage in a ferret model of ocular hypertension. *Jpn J Ophthalmol.* 2022 Mar;66(2): 205-212.
3. Ono T, Iwasaki T, Terada Y, Miyai T, Mori Y, Nejima R, Honma T, Aihara M, Miyata K. Corneal Toxicity After Stinging by a Sea Anemone, *Anthopleura uchidai*: A Case Report With Confirmation by In Vitro Study. *Cornea.* 2022 Aug 1;41(8):1035-1037.
4. Suzuki T, Obata R, Inoue T, Ueta Y, Azuma K, Tate H, Kitamoto K, Otaki C, Hashimoto Y, Aihara M, Tachi N. Intravenous lipo-prostaglandin E1 administration for patients with acute central retinal artery occlusion. *BMJ Open Ophthalmol.* 2022 May;7(1):e001014.
5. Nemoto H, Honjo M, Okamoto M, Sugimoto K, Aihara M. Potential Mechanisms of Intraocular Pressure Reduction by Micropulse Transscleral Cyclophotocoagulation in Rabbit Eyes. *Invest Ophthalmol Vis Sci.* 2022 Jun 1;63(6):3.
6. Azuma K, Koumura T, Iwamoto R, Matsuoka M, Terauchi R, Yasuda S, Shiraya T, Watanabe S, Aihara M, Imai H, Ueta T. Mitochondrial glutathione peroxidase 4 is indispensable for photoreceptor development and survival in mice. *J Biol Chem.* 2022 Apr;298(4):101824.
7. Fujita A, Hashimoto Y, Matsui H, Yasunaga H, Aihara M. Recent Trends in Treatment and Associated Costs of Primary Angle-Closure Glaucoma: A Retrospective Cohort Study. *Ophthalmol Glaucoma.* 2022 Oct 15:S2589-4196(22)00201-0.
8. Hashimoto Y, Okada A, Matsui H, Yasunaga H, Aihara M, Obata R. Recent trends in anti-vascular endothelial growth factor intravitreal

- injections: a large claims database study in Japan. *Jpn J Ophthalmol*. 2022 Dec 12;1-10.
9. Chen LW, Ono T, Hashimoto Y, Tsuneya M, Abe Y, Omoto T, Taketani Y, Toyono T, Aihara M, Miyai T. Regular and irregular astigmatism of bullous keratopathy using Fourier harmonic analysis with anterior segment optical coherence tomography. *Sci Rep*. 2022 Oct 25;12(1):17865.
10. Tsuneya M, Chen LW, Ono T, Hashimoto Y, Kitamoto K, Taketani Y, Toyono T, Aihara M, Miyai T. UbiA prenyltransferase domain-containing protein 1 (UBIAD1) variant c.695 A > G identified in a multigenerational Japanese family with Schnyder corneal dystrophy. *Jpn J Ophthalmol*. 2022 Nov 11.
11. Sakata R, Fujishiro T, Saito H, Nakamura N, Honjo M, Shirato S, Miyamoto E, Yamada Y, Aihara M. Prostaglandin-Associated Periorbitopathy Symptom Alleviation After Switching Prostaglandin F Receptor Agonist to EP2 Receptor Agonist in Patients with Glaucoma. *J Ocul Pharmacol Ther*. 2022 Oct 31.
12. Aoyama Y, Sakata R, Fujishiro T, Honjo M, Shirato S, Aihara M. Changes in corneal endothelial cell density after initial Ex-PRESS drainage device implantation and its relating factors over 3 years. *Eye (Lond)*. 2022 Jan 10.
13. Asahina Y, Hashimoto H, Aihara M, Noie T, Morikawa T. Impact of Neoadjuvant Chemotherapy on SATB2 Expression in Colorectal Carcinomas: SATB2 Positivity is Preserved in Most Cases, but Down-Expressed in Effective Cases of Chemotherapy. *Int J Surg Pathol*. 2022 Mar 27;10668969221088881.
14. Akiyama K, Ono T, Ishii H, Chen LW, Kitamoto K, Toyono T, Yoshida J, Aihara M, Miyai T. Impact of rigid gas-permeable contact lens on keratometric indices and corneal thickness of keratoconus eyes examined with anterior segment optical coherence tomography. *PLoS One*. 2022 Jul 8;17(7):e0270519.
15. Hashimoto Y, Yamana H, Iwagami M, Ono S, Takeuchi Y, Michihata N, Uemura K, Yasunaga H, Aihara M, Kaburaki T. Ocular Adverse Events after Coronavirus Disease 2019 mRNA Vaccination: Matched Cohort and Self-Controlled Case Series Studies Using a Large Database. *Ophthalmology*. 2022 Oct 26:S0161-6420(22)00832-6.
16. Azuma K, Nomura Y, Kitamoto K, Hashimoto Y, Fujino R, Ueda K, Inoue T, Obata R. Locational agreement of near-infrared autofluorescence with choroidal vascular hyperpermeability in central serous chorioretinopathy. *Retina*. 2022 Nov 1; 42(11):2203-2209.
17. Shirahama S, Tanaka R, Kaburaki T. Anterior Uveitis Associated with Human Herpesvirus 7 Infection Diagnosed by Multiplex Polymerase Chain Reaction Assay: A Case Report. *Ocul Immunol Inflamm*. 2022 Feb 24;1-3.
18. Ishii H, Yoshida J, Toyono T, Yamagami S, Usui T, Miyai T. Three-year results of accelerated transepithelial cross-linking (30 mW/cm² × 3 min) for keratoconus: a prospective study. *BMJ Open Ophthalmol*. 2022 Feb 8;7(1):e000827.
19. Shiraya T, Araki F, Nakagawa S, Ueta T, Totsuka K, Abe H, Naito Y, Toyama T, Sugimoto K, Kato S. Differential gene expression analysis using RNA sequencing: retinal pigment epithelial cells after exposure to continuous-wave and subthreshold micropulse laser. *Jpn J Ophthalmol*. 2022 Sep;66(5):487-497.
20. Shiraya T, Araki F, Nakagawa S, Ueta T, Totsuka K, Abe H, Naito Y, Toyama T, Sugimoto K, Kato S. Differential gene expression analysis using RNA sequencing: retinal pigment epithelial cells after exposure to continuous-wave and subthreshold micropulse laser. *Jpn J Ophthalmol*. 2022 Sep;66(5):487-497.
21. Toyama T, Kawai H, Hashimoto Y, Azuma K, Shiraya T, Numaga J, Obuchi S, Ueta T; OTASSHA Study Group. Macular and peripapillary retinal nerve fiber layer thinning in eyes with prediabetes in the elderly population: OTASSHA study. *Graefes Arch Clin Exp Ophthalmol*. 2022 Dec 1.
22. Wang Y, Toyama T, Hashimoto Y, Kawai H, Azuma K, Shiraya T, Kato S, Watanabe Y, Hirano H, Fujiwara Y, Ihara K, Kim H, Numaga J, Obuchi S, Ueta T. ASSOCIATION OF PREDIABETES WITH RETINAL MICROVASCULATURE ON SWEPT-SOURCE OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY IN THE ELDERLY: OTASSHA

Study. *Retina*. 2022 Jun 1;42(6):1130-1136

23. Aoki S, Imaizumi H. Simultaneous development of full-thickness macular hole and neovascular age-related macular degeneration. *Am J Ophthalmol Case Rep*. 2022 Jan 22;25:101325.
24. Ozawa R, Azuma K, Nomura Y, Murata H, Asaoka R, Kitamoto K, Ueda K, Inoue T, Obata R. Association between retinal sensitivity and the presence of quiescent choroidal neovascularization in pachychoroid diseases. *PLoS One*. 2022 Jul 26;17(7):e0271543.

Department of Otorhinolaryngology and Head & Neck Surgery

Professor

Kenji Kondo, M.D., Ph.D.

Associate Professor

Akinori Kashio, M.D., Ph.D.

Rumi Ueha, M.D., Ph.D. (Swallowing Center)

Lecturer

Yuki Saito, M.D., Ph.D.

Chisato Fujimoto, M.D., Ph.D.

Research Associate

Osamu Fukuoka, M.D.

Makoto Kinoshita, M.D., Ph.D.

Takao Goto, M.D.

Taku Sato, M.D.

Teru Kamogashira, M.D., Ph.D.

Kei Ogawa, M.D., Ph. D.

Hironobu Nishijima, M.D., Ph.D.

Ryoji Kagoya , M.D., Ph.D.

Kenya Kobayashi, M.D., Ph.D.

Shinji Urata, M.D., Ph. D.

Hajime Koyama, M.D., Ph. D.

Homepage <http://utokyo-ent.org/>

Introduction and Organization

The Department of Otorhinolaryngology was founded in 1899 by Prof. Waichiro Okada who studied in Germany. This is the first department of otorhinolaryngology of the national university in Japan. Our department covers all otorhinolaryngological diseases and associated systemic diseases and has specialized clinics in middle ear and inner ear diseases, hearing impaired infant and children, adult and elderly patients, facial palsy, vertigo and balance disorders, olfactory disorders and paranasal diseases, voice and speech disorders, swallowing and airway disorders, aphasia, central auditory disorders and head & neck

cancers.

A professor, associate professors, lecturers (assistant professors), research associates, and international clinical fellows participate in surgery, out-patient and in-patient care as well as research and educational activities. Moreover 6 Japanese graduate students participate in basic research.

Weekly preoperative and postoperative conferences are held to discuss surgical cases in detail. Special lectures on leading research activities are presented by invited guests. A journal club is held to introduce current research papers.

Clinical activities

In the out-patient clinic, general and special services are provided to approximately 150 out-patients on a daily basis in all areas of otorhinolaryngology and related specialties, and approximately 300 new patients visit monthly.

In the inpatient hospital, 27 beds are prepared for patients under the supervision of lecturers and senior research associates from each subspecialty group including head & neck surgery, middle ear surgery and cochlear implant surgery, voice and swallowing surgery, and paranasal surgery and other minor surgery. Preoperative and postoperative problems are checked and discussed by each group, the professor's and associate professor's rounds. Approximately 1000 operations are performed annually.

Cochlear implant surgery over 400 cases has been performed for infants, children and adult patients with profound hearing loss and is very successful to provide new hearing. Head and neck surgery is performed to extirpate malignant tumor with neighboring tissues and reconstruct upper respiratory and swallowing functions at one stage operation cooperating with plastic surgeons. Reconstructive surgery of microtia and atresia to reconstruct external ear is routinely performed with plastic surgeons.

Auditory brainstem response is routinely examined in order to diagnose peripheral and central deafness in neonates, infants and children.

Teaching activities

Serial lectures on otorhinolaryngology head and neck surgery, and special lectures on its current topics are provided to the fourth year and the fifth/sixth year of medical students, respectively.

Clinical training is provided for the sixth year class of medical students on a one-to-one basis with staff doctors. They are requested to write reports on a clinical case or a clinical problem. The students participate to see surgery, special clinics and clinical examinations such as otoscope, fiberscope, pure-tone audiometry, auditory brainstem response, and caloric test. They are questioned on many aspects of clinical problems in seminars by a professor and associate professors.

Research activities

Clinical and basic research activities are highly encouraged. Clinical research, which is supervised by senior doctors, is very actively pursued even by young residents. Case reports presentation and writing skills are regarded as important experience in order to develop young doctors' research activity and investigate important findings in patients. The clinical research is related to ear surgery, neurotology, audiology, head and neck surgery, laryngology, bronchoesophagology and rhinology and is related to case research, clinical statistics and clinical electrophysiology. Basic research is also encouraged to solve essence of clinical problems and to elucidate basic phenomena or anatomical and cellular structures. Our research topics cover:

- 1) Morphology and neurophysiology of the inner ear focusing on sensory neural deafness
- 2) Regeneration of inner ear hair cells
- 3) Liquid biopsy of perilymph via round window membrane
- 4) Prediction of hearing outcome in tympanoplasty and cochlear implant using machine learning
- 5) Speech perception and language development in deaf children
- 6) Effects of cochlear implantation on central neural plasticity using AMPA receptor imaging
- 7) Surgical anatomical analysis of the middle and inner ear using imaging and endoscopy
- 8) Analysis of balance disorders using various vestibular function tests
- 9) Development of new testing methods for balance disorders
- 10) Development of a new treatment for balance disorders using vestibular electrical stimulation
- 11) Prediction and pathophysiology of vestibular disorders using machine learning
- 12) Elucidation of the pathophysiology of vestibular migraine
- 13) Development of a novel treatment for persistent perceptual posture-induced vertigo
- 14) Elucidation of the mechanism of postural control in patients with vestibular disorders using mathematical models
- 15) Establishment of animal models of vestibular

disorders and development of treatment methods

16) Electrophysiological prognostic studies of facial nerve palsy

17) Development, regeneration, and aging of the olfactory epithelium

18) Analysis of the physiology and pathophysiology of olfactory reception

19) Pathogenesis and treatment of olfactory disorders

20) Development of surgical methods based on computational modeling of intranasal airflow

21) Nasal mucosa damage and central nervous system impairment caused by COVID-19

22) The odorant metabolic capacity of nasal mucus.

23) Development of animal models of ECRS.

24) Research on aspiration prevention surgeries based on swallowing function and background disease conditions

25) Research on swallowing impairment in patients with lung transplants

26) Elucidation of swallowing mechanisms using pathological and electrophysiological analysis and VR system

27) Research on esophageal motility in neuromuscular disorders

28) Research on esophageal motility in systemic sclerosis

29) Evaluation of swallowing physiology with pharyngo-esophageal high-resolution manometry

30) Pathophysiological analysis and prevention/regeneration of vocal cord paralysis and inflammation using animal models

31) Gene expression analysis of recurrent respiratory papillomatosis

32) Analysis of kinetics of voice disorders and development of new therapeutic approaches

33) Investigating of prognostic factors for head and neck cancer

34) Relationship between alcohol consumption and viral infection in the carcinogenesis of pharyngeal cancer

35) Exploration of targeted therapy through comprehensive genomic profiling

36) Exploration of predictors of response to immune checkpoint inhibitors

37) Development of novel therapies such as head and neck alluminox treatment and transoral robotic surgery

38) Development of novel therapies for head and neck

cancer through multicenter collaborative research

Various clinical and basic research is conducted by staff, residents, and graduate students as well as doctors at affiliated hospitals.

References

1. Abe C, Katayama C, Bazek M, Nakamura Y, Ohbayashi K, Horii K, Fujimoto C, Tanida M, Iwasaki Y, Inoue T, Nin F, Morita H. Repeated activation of C1 neurons in medulla oblongata decreases anti-inflammatory effect via the hypofunction of the adrenal gland adrenergic response. *Brain Behav Immun*. 111:138-50. 2023
2. Abe C, Katayama C, Ohbayashi K, Horii K, Ogawa B, Fujimoto C, Iwasaki Y, Nin F, Morita H. Galvanic vestibular stimulation-induced activation of C1 neurons in medulla oblongata protects against acute lung injury. *Am J Physiol Regul Integr Comp Physiol*. 324(2):R152-R60. 2023
3. Ariizumi Y, Hanai N, Asakage T, Seto A, Tomioka T, Miyabe J, Kessoku H, Mukaigawa T, Omura G, Teshima M, Nishikawa D, Saito Y, Asada Y, Fujisawa T, Makino T, Nishino H, Sano D, Nakahira M, Tokashiki K, Uemura H, Ueda T, Sakai A, Masuda M, Tsujikawa T, Hiei Y, Nishio N, Matsui H, Kiyota N, Homma A. Extent of thyroidectomy and paratracheal lymph node dissection in total pharyngolaryngectomy for pyriform sinus cancer, and recurrence, survival, and postoperative hypoparathyroidism: A multicenter retrospective study. *Head Neck*. 2023 Nov 13. doi: 10.1002/hed.27572. Online ahead of print.
4. Eguchi K, Kobayashi K, Honma Y, Ryo E, Sakyo A, Yokoyama K, Watanabe T, Aihara Y, Sakai A, Matsumoto Y, Sakai T, Omura G, Yatabe Y, Yoshimoto S, Mori T. Clinical and pathological features of second primary neoplasms arising in head and neck reconstructive skin flaps. *Sci Rep*. 13(1):11214. 2023
5. Eguchi K, Omura G, Murakami N, Honma Y, Yokoyama K, Watanabe T, Aihara Y, Sakai A, Matsumoto Y, Sakai T, Kobayashi K, Igaki H, Yoshimoto S. Comparison of Survival Outcomes

- Between Larynx-Preserving Open Partial Pharyngectomy and Radiotherapy or Chemoradiotherapy in Patients with Hypopharyngeal Squamous Cell Carcinoma: A Single-Center Retrospective Analysis with Inverse Probability of Treatment Weighting Adjustments. *Ann Surg Oncol*. 30(11):6867-74. 2023
6. Eguchi K, Omura G, Shimoi T, Kageyama D, Igaki H, Abe Y, Watanabe T, Aihara Y, Sakai A, Matsumoto Y, Sakai T, Yonemori K, Mori T, Yoshida A, Yoshimoto S. BCOR-CCNB3 sarcoma arising in the pharynx. *Auris Nasus Larynx*. 50(4):618-22. 2023
 7. Fujimoto C, Kawahara T, Kinoshita M, Kamogashira T, Oka M, Ichijo K, Koda K, Yamasoba T, Iwasaki S. Inter-day and intra-day variations in effective intensity of noisy galvanic vestibular stimulation to improve postural stability in bilateral vestibulopathy. *J Vestib Res*. 33(6):423-9. 2023
 8. Fujimoto C, Oka M, Ichijo K, Kinoshita M, Kamogashira T, Sugawara K, Kawahara T, Yamasoba T. The effect of self-management vestibular rehabilitation on persistent postural-perceptual dizziness. *Laryngoscope Investig Otolaryngol*. 8(4):1014-20. 2023
 9. Fujisawa K, Miyamoto S, Saito Y, Suzuki S, Okazaki M. Transverse Cervical Artery for Head and Neck Reconstruction with Free Jejunal Flaps: A Retrospective Study of Computed Tomography Angiography. *J Reconstr Microsurg*. 2023
 10. Fujita T, Sakai K, Uehara N, Hoshi Y, Mori A, Koyama H, Sato M, Saito K, Osaki Y, Nishio K, Doi K. Genetic variants of cancer-associated genes analyzed using next-generation sequencing in small sporadic vestibular schwannomas. *Oncol Lett*. 25(3):121. 2023
 11. Fukuoka O, Saito Y, Mukai T, Hayashi T, Yamamura K, Sakai T, Kobayashi K, Akashi K, Yoshida M, Ando M, Yamasoba T. Efficacy of Chemotherapy After Immune Checkpoint Inhibitor Discontinuation in Head and Neck Cancer. *Laryngoscope*. 134(1):228-35. 2024
 12. Goto T, Ueha R, Sato T, Yamasoba T. Effects of early local administration of high-dose bFGF on a recurrent laryngeal nerve injury model. *J Otolaryngol Head Neck Surg*. 52(1):47. 2023
 13. Han B, Kamogashira T, Kikuta S, Yamasoba T. Endoplasmic reticulum stress associated with lead (Pb)-induced olfactory epithelium toxicity in an olfactory dark basal cell line. *FEBS Open Bio*. 13(12):2162-71. 2023
 14. Hanakita S, Shin M, Hasegawa H, Shojima M, Ohara K, Shinya Y, Kawashima M, Kondo K, Saito N. Endoscopic Extended Transsphenoidal Surgery Aiming for Radical Resection of Skull Base Tumors Involving Cavernous Sinus: Assessment of Resectability and Risks of Complications. *Oper Neurosurg (Hagerstown)*. 25(3):260-8. 2023
 15. Hara M, Ueha R, Sato T, Goto T, Yoshizaki A, Sumida H, Sato S, Yamasoba T. Clinical Risk Factors for Dysphagia and Esophageal Dysmotility in Systemic Sclerosis. *J Clin Med*. 12(10). 2023
 16. Hasegawa H, Shin M, Shinya Y, Kashiwabara K, Kikuta S, Kondo K, Saito N. Long-term Outcomes of Non-vascularized Multilayer Fascial Closure Technique for Dural Repair in Endoscopic Transnasal Surgery: Efficacy, Durability, and Limitations. *World Neurosurg*. 175:e97-e107. 2023
 17. Hasegawa H, Shinya Y, Ono M, Kikuta S, Kondo K, Saito N. Kashimé: A Novel Knotless Surgical Suture to Simplify Dural Stitches in Endoscopic Transnasal Surgery. *Oper Neurosurg (Hagerstown)*. 24(4):417-24. 2023
 18. Homma A, Mikami M, Matsuura K, Onimaru R, Yoshida D, Shinomiya H, Ohkoshi A, Hayashi R, Saito Y, Tachibana H, Shiga K, Ueda T, Uemura H, Nakamura K, Fukuda H, Head, Neck Cancer Study Group of the Japan Clinical Oncology G. Dose-Finding and Efficacy Confirmation Trial of the Superselective Intra-arterial Infusion of Cisplatin and Concomitant Radiation Therapy for Locally Advanced Maxillary Sinus Cancer (JCOG1212): Results of the Efficacy Confirmation Phase in Patients with T4aN0M0. *Int J Radiat Oncol Biol Phys*. 2023
 19. Hosokawa T, Tanami Y, Sato Y, Adachi N, Asanuma H, Oguma E. Sonographic Findings of Cervical Chondrocutaneous Branchial

- Remnants-A Comparison With Dermal Lesions/ Cysts and a Literature Review: A Pilot Study. *J Ultrasound Med.* 9999:1-12. 2023
20. Hosokawa T, Tanami Y, Sato Y, Adachi N, Asanuma H, Oguma E. Clinical audit of ultrasonography for detecting sialoliths in the submandibular gland in paediatric patients: A comparison to computed tomography and magnetic resonance imaging. *Australas J Ultrasound Med.* 12370:1-11. 2023
21. Ichijo K, Oka M, Koda K, Kamogashira T, Kinoshita M, Kawahara T, Takashima I, Demura S, Yamasoba T, Fujimoto C. Analysis of postural stability using foam posturography in patients with persistent postural-perceptual dizziness. *J Vestib Res.* 2023
22. Inamoto Y, Ueha R, Fernandez GM. Emerging Dysphagia Technologies: Swallowing CT. *Current Otorhinolaryngology Reports* 11:154–160. 2023
23. Ito A, Nakaya M, Tada K, Kumada J, Kida W, Inayoshi Y. Is tooth conservation possible in odontogenic sinusitis? Prospective evaluation of affected teeth condition-based protocol. *Acta Otolaryngol.* 17:1–7, 2023
24. Ito A, Fukuda S, Shimozawa M, Abe K, Kumada J, Nakaya M. Benefits of amplification for unaided speech discrimination in age-related hearing loss with flat type audiogram. *Auris Nasus Larynx* 50:62–69, 2023
25. Iwanami T, Kagoya T, Isozaki K, Ito K. Surgical drainage of pediatric gas-containing orbital subperiosteal abscess. *Acta Oto-Laryngologica Case Reports* <https://doi.org/10.1080/23772484.2023.2169148>. 2023
26. Kakigi A, Egami N, Fujita T, Uehara N, Yokoi J, Koda K, Nibu KI, Yamashita S, Yamasoba T. Live Imaging of the Dehydration Effect of Isosorbide on the Normal and Hydropic Guinea Pig Cochleae Using Optical Coherence Tomography. *Otol Neurotol.* 44(8):833-7. 2023
27. Kaneoka A, Inokuchi H, Ueha R, Sato T, Goto T, Yamauchi A, Seto Y, Haga N. Longitudinal Analysis of Dysphagia and Factors Related to Postoperative Pneumonia in Patients Undergoing Esophagectomy for Esophageal Cancer. *Dysphagia.* 2023
28. Kaneoka A, Ogino A, Inokuchi H, Shichiri T, Matsuzaki A, Sato T, Goto T, Yamauchi A, Saito Y, Ueha R. The use of a patient booklet to enhance adherence to prophylactic exercises for patients undergoing chemoradiation therapy for head and neck cancer. *The Japan Society of Logopedics and phoniatric* 64:85-95. 2023
29. Kashio A, Yamada C, Yasuhara K, Kamogashira T, Someya S, Yamasoba T. Taurine, Coenzyme Q(10), and Hydrogen Water Prevents Germanium Dioxide-Induced Mitochondrial Dysfunction and Associated Sensorineural Hearing Loss in mouse. *Hear Res.* 428:108678. 2023
30. Katsuno T, Ueha R, Fujisaki A, Unno T, Cotaoco C, Kaneoka A, Koyama M, Sato T, Goto T, Kondo K. Differences in residual volume above different tracheostomy tube cuffs depending on tube structure, tube tilt angle, and liquid viscosity. *Eur Arch Otorhinolaryngol.* 281(1):311-7. 2023
31. Katsushika M, Kamogashira T, Koizumi M, Kuriyama M, Arimoto K, Miyano K, Ishimoto S. Retrospective study of risk factors for tympanic membrane perforation in the early period after intratympanic steroid injection. *Auris Nasus Larynx.* 50(5):714-9. 2023
32. Kikuta S, Han B, Yamasoba T. Heterogeneous Damage to the Olfactory Epithelium in Patients with Post-Viral Olfactory Dysfunction. *J Clin Med.* 12(15). 2023
33. Kinoshita M, Fujimoto C, Iwasaki S, Kondo K, Yamasoba T. Oral Administration of TrkB Agonist, 7, 8-Dihydroxyflavone Regenerates Hair Cells and Restores Function after Gentamicin-Induced Vestibular Injury in Guinea Pig. *Pharmaceutics.* 15(2). 2023
34. Kishimoto-Urata M, Urata S, Nishijima H, Baba S, Fujimaki Y, Kondo K, Yamasoba T. Predicting synkinesis caused by Bell's palsy or Ramsay Hunt syndrome using machine learning-based logistic regression. *Laryngoscope Investig Otolaryngol.* 8(5):1189-95. 2023
35. Kobayashi K, Hanai N, Yoshimoto S, Saito Y, Homma A. Current topics and management of head and neck sarcomas. *Jpn J Clin Oncol.* 53(9):743-56. 2023

36. Kobayashi K, Kawazu M, Yoshimoto S, Ueno T, Omura G, Saito Y, Ando M, Ryo E, Sakyo A, Yoshida A, Yatabe Y, Mano H, Mori T. Genome Doubling Shapes High-Grade Transformation and Novel EWSR1::LARP4 Fusion Shows SOX10 Immunostaining in Hyalinizing Clear Cell Carcinoma of Salivary Gland. *Lab Invest*. 103(10):100213. 2023
37. Kobayashi K, Saito Y, Kage H, Fukuoka O, Yamamura K, Mukai T, Oda K, Yamasoba T. CDK12 alterations and ARID1A mutations are predictors of poor prognosis and therapeutic targets in high-grade salivary gland carcinoma: analysis of the National Genomic Profiling Database. *Jpn J Clin Oncol*. 53(9):798-807. 2023
38. Kobayashi K, Saito Y, Kamogashira T, Kage H, Fukuoka O, Yamamura K, Mukai T, Oda K, Yamasoba T. Survival analysis of high-grade salivary gland carcinoma adjusted for length bias due to delay in comprehensive genomic profiling. *Jpn J Clin Oncol*. 53(11):1092-3. 2023
39. Koda K, Yasuhara K. Thyroglossal duct carcinoma with submental lymph node metastasis. *Asian Journal of Surgery* 8:3152-3153. 2023
40. Koike-Ieki M, Kagoya R, Toma-Hirano M, Sasajima Y, Ito K. Improvement of eosinophilic chronic rhinosinusitis after infection with severe acute respiratory syndrome corona virus 2 during dupilumab therapy: A case report. *Front Allergy*. 4:1053777. 2023
41. Koike-Ieki M, Kida W. Laryngeal Candidiasis. *N Engl J Med*. Jul 20;389(3):e5. 2023 doi: 10.1056/NEJMicm2215136.
42. Koyama H, Kashio A, Nishimura S, Takahashi H, Iwasaki S, Doi K, Nakagawa T, Ito K, Yamasoba T. Etiology, Severity, Audiogram Type, and Device Usage in Patients with Unilateral Moderate to Profound Sensorineural Hearing Loss in Japan. *J Clin Med*. 12(13). 2023
43. Koyama H, Kashio A, Uranaka T, Matsumoto Y, Yamasoba T. Application of Machine Learning to Predict Hearing Outcomes of Tympanoplasty. *Laryngoscope*. 133(9):2371-8. 2023
44. Koyama M, Ueha R, Sato T, Goto T, Yamauchi A, Kaneoka A, Suzuki S, Nito T, Yamasoba T. Aspiration Prevention Surgery: Clinical Factors Associated With Improvements in Oral Status Intake and Suction Frequency. *Otolaryngol Head Neck Surg*. 168(5):1146-55. 2023
45. Koyama S, Mori E, Ueha R. Insight into the mechanisms of olfactory dysfunction by COVID-19. *Auris Nasus Larynx*. 50(4):490-8. 2023
46. Matsumoto N, Kagoya R, Yasui M, Uozaki H, Ito K. A Case of Fungal Maxillary Sinusitis Extending to the Contralateral Side Through the Nasal Septum. *Cureus*. 15(5):e39548. 2023
47. Matsumoto N, Kashio A, Yoshida M, Kondo K, Miyamoto S, Okazaki M, Ikemura M, Ushiku T, Yamasoba T. Cholesterol granuloma in facial nerve canal presenting with facial nerve paralysis. *Auris Nasus Larynx*. 50(5):799-804. 2023
48. Matsumoto N, Toma-Hirano M, Yasui T, Ito K. Disseminated herpes zoster in an immunocompetent young adult: A rare complication of Ramsay Hunt syndrome. *Acta Otolaryngologica Case Reports* <https://doi.org/10.1080/23772484.2023.2217343>. 2023
49. Monobe H, Nakahishi W, Kawawaki W, Tsuda Y. Diagnosis of Patients Presenting with Vertigo, Headache, and Epileptic Seizure: Evaluating Vestibular Patients by Using Cervical Vestibular Evoked Myogenic Potential and Auditory Middle Latency Responses in the Clinical Setting. *J Int Adv Otol*. 19(1):61-5. 2023
50. Murofushi T, Monobe H, Ushio M. Isolated bilateral posterior semicircular canal hypofunction: comparison with bilateral vestibulopathy. *Acta Otolaryngol*. 143(8):687-91. 2023
51. Naito R, Watanabe Y, Naito A, Sugawara K, Nakata Y, Kamiyama T, Okiyama R, Yokochi F, Isozaki E, Yamasoba T, Takahashi K. Visual fixation suppression of caloric nystagmus in progressive supranuclear palsy - A comparison with Parkinson's disease. *J Vestib Res*. 33(6):385-401. 2023
52. Nakagawa Y, Ushidome K, Masuda K, Igarashi K, Matsumoto Y, Yamasoba T, Anraku Y, Takai M, Cabral H. Multi-Armed Star-Shaped Block Copolymers of Poly(ethylene glycol)-Poly(furfuryl glycidol) as Long Circulating Nanocarriers. *Polymers (Basel)*. 15(12). 2023
53. Nomura T, Horikoshi T, Kitano Y, Yamada M, Kondo K, Kikuchi S. The morphometrical

- evaluation after uvulopalatopharyngoplasty. *Sleep Breath*. 2023
54. Ogasawara N, Kikuchi D, Tanaka M, Ochiai Y, Okamura T, Hayasaka J, Suzuki Y, Mitsunaga Y, Nomura K, Odagiri H, Yamashita S, Matsui A, Watanabe K, Takeda H, Hoteya S. Long-term outcome of cervical lymph node metastasis in superficial pharyngeal squamous cell carcinoma after endoscopic submucosal dissection. *Gastrointest Endosc*. 98(4):524-33 e2. 2023
 55. Oka M, Ichijo K, Koda K, Kamogashira T, Kinoshita M, Igarashi K, Kawahara T, Takashima I, Yamasoba T, Fujimoto C. Preceding Balance Disorders Affect Vestibular Function in Persistent Postural-Perceptual Dizziness. *J Clin Med*. 12(7). 2023
 56. Omura G, Honma Y, Matsumoto Y, Shinozaki T, Itoyama M, Eguchi K, Sakai T, Yokoyama K, Watanabe T, Ohara A, Kato K, Yoshimoto S. Transnasal photoimmunotherapy with cetuximab sarotalocan sodium: Outcomes on the local recurrence of nasopharyngeal squamous cell carcinoma. *Auris Nasus Larynx*. 50(4):641-5. 2023
 57. Omura G, Namikawa K, Sakai T, Eguchi K, Matsumoto Y, Sakai A, Kobayashi K, Nakano E, Ogata D, Matsumoto F, Mori T, Yamazaki N, Yoshimoto S. Clinical outcomes of head and neck mucosal melanoma treated with surgery: a single-center study in Japan. *Jpn J Clin Oncol*. 53(11):1045-50. 2023
 58. Omura G, Yoshimoto S, Rikitake R, Eguchi K, Nakamizo M, Nibu KI. Comparison of survival outcomes between adolescent and young adults and older adults with tongue squamous cell carcinoma: a nationwide database study using the head and neck cancer registry of Japan. *Int J Clin Oncol*. 28(2):221-8. 2023
 59. Oyama S, Adachi-Katayama M, Okamoto K, Jin C, Yamamura K, Saito Y, Kanematsu A, Otani A, Wakimoto Y, Oyabu T, Jubishi D, Hashimoto H, Harada S, Okugawa S, Moriya K. Preseptal cellulitis with *Streptococcus pyogenes* complicated by streptococcal toxic shock syndrome: A case report and review of literature. *J Infect Chemother*. 29(8):783-6. 2023
 60. Rai Y, Umekawa M, Shinya Y, Hasegawa H, Katano A, Kondo K, Shinozaki-Ushiku A, Saito N. Stereotactic radiosurgery for recurrent skull base polymorphous adenocarcinoma invading the cavernous sinus: illustrative case. *J Neurosurg Case Lessons*. 5(19). 2023
 61. Sahara T, Kashio A, Kamogashira T, Ogata E, Akamatsu Y, Yamasoba T. Cochlear implantation for progressive hearing loss caused by an A8296G mutation in mitochondrial DNA. *Auris Nasus Larynx*. 51(1):82-5. 2023
 62. Saito Y, Kage H, Kobayashi K, Yoshida M, Fukuoka O, Yamamura K, Mukai T, Oda K, Yamasoba T. TERT promoter mutation positive oral cavity carcinomas, a clinically and genetically distinct subgroup of head and neck squamous cell carcinomas. *Head Neck*. 45(12):3107-18. 2023
 63. Saito Y, Kobayashi K, Fukuoka O, Sakai T, Yamamura K, Ando M, Kondo K. Ultra-high combined positive score and high serum albumin are favorable prognostic biomarkers for immune checkpoint inhibitors in head and neck squamous cell carcinoma. *Head Neck*. 46(2):367-77. 2024
 64. Sakaguchi Y, Saito Y, Ando M, Yoshida M, Fukuoka O, Kobayashi K, Kubota D, Ohki D, Mizutani H, Niimi K, Tsuji Y, Fujishiro M, Yamasoba T. Risk factors for incomplete resection with pharyngeal endoscopic submucosal dissection and long-term prognosis after resection. *Surg Endosc*. 37(5):3593-601. 2023
 65. Sakata A, Kashio A, Koyama M, Urata S, Koyama H, Yamasoba T. Hearing and Hearing Loss Progression in Patients with GJB2 Gene Mutations: A Long-Term Follow-Up. *Int J Mol Sci*. 24(23). 2023
 66. Sato D, Hasegawa H, Nishijima H, Kawase K, Okamoto K, Iwasaki A, Shinya Y, Abe M, Miyazaki Y, Saito N. Intracranial aspergilloma mimicking metachronous meningioma following transsphenoidal removal of a tuberculum sellae meningioma: illustrative case. *J Neurosurg Case Lessons*. 5(5). 2023
 67. Shimada Y, Suyama Y, Koizumi M, Hagiwara K. Laryngeal edema in drug reaction with eosinophilia and systemic symptoms syndrome

- due to sulfasalazine. *Int J Rheum Dis.* 26(11): 2317-9. 2023
68. Suto A, Ueha R, Ogura T, Maeda E, Tatebayashi M, Shimada D, Koyama M, Sato T, Goto T, Yamauchi A, Yamasoba T. Swallowing computed tomography and virtual reality as novel imaging modalities for the diagnosis of clicking larynx: Two case reports. *Auris Nasus Larynx.* 50(3):468-72. 2023
 69. Takaki K, Nozaki E, Kanai T, Hautasaari A, Kashio A, Sato D, Kamogashira T, Uranaka T, Urata S, Koyama H, Yamasoba T, Kawahara Y. asEars: Designing and Evaluating the User Experience of Wearable Assistive Devices for Single-Sided Deafness. *Proceedings of the 2023 CHI Conference on Human Factors in Computing Systems.* 1-17:2023
 70. Tanaka T, Ushio M, Terada H, Takanami T, Kan S, Masuda H, Ochi K, Ikeda H, Yoshino R, Ohta Y. The Caloric Test Is More Consistent With the Presence of Endolymphatic Hydrops Than the Vestibular-Evoked Myogenic Potential Test in Meniere's Disease. *Cureus.* 15(12):e51384. 2023
 71. Taniguchi K, Tsutsumiuchi K, Sagara Y, Tayama N. Prevention of cuff injury of the intubation tube by blunt window opening in tracheostomy. *Glob Health Med.* 5(6):381-4. 2023
 72. Tarnutzer AA, Seo T, Fujimoto C, Straumann D, Murofushi T. Editorial: Impacts of VEMP and VHIT on the diagnosis of vestibular diseases. *Front Neurol.* 14:1244367. 2023
 73. Toma-Hirano M, Kagoya R, Ito K. Recurrent facial baroparesis on airplane flights relieved by endoscopic sinus surgery: a case report. *Acta Oto-Laryngologica Case Reports* 8:100-103 2023.
 74. Tsunoda K, Mochimaru T, Takazawa M, Nakazawa R, Komai N. Dysphonia After Taking Dietary Supplements. *Am J Med.* 136(5):e85-e6. 2023
 75. Ueha R, Cotaoco C, Kondo K, Yamasoba T. Management and Treatment for Dysphagia in Neurodegenerative Disorders. *J Clin Med.* 13(1). 2023
 76. Ueha R, Magdayao RB, Koyama M, Sato T, Goto T, Yamasoba T. Aspiration prevention surgeries: a review. *Respir Res.* 24(1):43. 2023
 77. Urata S, Okabe S. Three-dimensional mouse cochlea imaging based on the modified Sca/eS using confocal microscopy. *Anat Sci Int.* 98(3): 309-17. 2023
 78. Ushio M, Kitazawa Y, Tamura Y, Yoshida T, Uchiyama M, Takanami T, Tanaka T, Ikemiyagi Y, Ikemiyagi F, Ohta Y. High Cardio-Ankle Vascular Index Values in Idiopathic Sudden Sensorineural Hearing Loss Patients Indicate Better Prognosis. *Cureus.* 15(11):e49400. 2023
 79. Ushio M, Tanaka T, Ikemiyagi F, Totsuka H, Takanami T, Ikemiyagi Y, Kitazawa Y, Nomura T, Ohta Y, Yoshida T. Higher Cardio-Ankle Vascular Index Values in Patients With Vestibular Neuritis May Indicate a Better Prognosis. *Cureus.* 15(11):e49151. 2023
 80. Wada S, Watanabe T, Ishii T, Ichinose Y, Rikitake R, Ogata D, Nakano E, Namikawa K, Yamazaki N, Higashi T. A retrospective study of sentinel lymph node biopsy for skin cancer in Japan: Comparison with breast cancer and evaluation of factors related to its use. *Cancer Med.* 12(23):21364-72. 2023
 81. Watanabe T, Rikitake R, Kakuwa T, Ichinose Y, Niino M, Mizushima Y, Ota M, Fujishita M, Tsukada Y, Higashi T. Time to Treatment Initiation for Six Cancer Types: An Analysis of Data from a Nationwide Registry in Japan. *World J Surg.* 47(4):877-86. 2023
 82. Yamakawa K, Nishijima H, Kubota A, Naruse H, Baba S, Fujimaki Y, Kondo K, Toda T, Yamasoba T. Clinical and electrophysiological findings of facial palsy in a case of hereditary gelsolin amyloidosis. *Auris Nasus Larynx.* 50(2): 305-8. 2023
 83. Yamamura K, Saito Y, Kobayashi K, Mukai T, Fukuoka O, Akashi K, Yoshida M, Ando M, Yamasoba T. p16 status and high-risk human papilloma virus infection in squamous cell carcinoma of the nasal vestibule. *Auris Nasus Larynx.* 50(6):942-7. 2023

Department of Rehabilitation Medicine

Professor

Toru Ogata, M.D.

※The following information is the same as that of the previous year for certain reasons.

Homepage <http://todaireh.umin.ne.jp>

Introduction and Organization

The Department of Rehabilitation Medicine was established by Ministry of Education, Culture, Sports, Science and Technology in April 2001. It is one of the newest fields in Graduate School of Medicine, the University of Tokyo. It belongs to the Sensory and Motor System Science Course of the Surgical Science Division. Current authorized staff is only one professor.

This department derives from the establishment of the physical therapy room in the central diagnostic and therapeutic sections in order to develop the clinical practice of rehabilitation medicine in 1963. The chair of professor was set up as a full-time director of the central rehabilitation service in 1984, but the formal title remained a physical therapy department.

Rehabilitation medicine is a newly established clinical section which was born in development of the modern principle of the medical health service by which it came to value the enhancement of not only adding years of patient's life but also adding life to the years. Regardless of the rapid expansion of needs, acknowledgment of rehabilitation medicine was delayed in the frame of the old-fashioned clinical departments. In our country, it was 1996 when the rehabilitation specialty was authorized as formal clinical practice by the former Ministry of Health and Welfare.

On the other hand, it was positioned as an assistance instructor in the sensory and motor system medicine department with shifting to the graduate

school course systems since 1995 to 97 in the University of Tokyo. Finally, the rehabilitation medicine field was installed in the sensory and motor system medicine department by a budget step of 2001. We have accepted the graduate school student formally since fiscal year 2001. However, the arrangement of additional teaching staff is not still materialized. Therefore, the staff of the graduate school is only one professor. Twenty students have entered the graduate school by 2020, and fifteen of them were granted Ph.D.

Clinical activities

The professor serves as a director of Rehabilitation Center, the University of Tokyo Hospital. The Rehabilitation Center and the Department of Rehabilitation Medicine are united and engage in clinical practice. We have at present no charged ward, and treat about 4,700 new referrals annually from almost all the departments of the university hospital. We always take charge of 250-300 patients corresponding about 25-30% of the whole number of inpatients. We also see 15 people per day at the outpatient rehabilitation setting. The numerical ratio of outpatient is being reduced in order to give priority to the clinical service corresponding to needs expansion of service to inpatients.

Teaching activities

We have provided several clinical curriculums on

rehabilitation medicine for 4th, 5th, and 6th year medical students since 1973. The systematic lecture series for 4th year medical students (M2) include the subjects on rehabilitation for disorders such as cerebrovascular disturbances, respiratory disorders, neuromuscular diseases, bone and joint diseases, and pediatric disorders as well as on outline of rehabilitation, and amputation/prostheses. We have provided a clinical practice in small group, so-called clinical clerkship for 5th and 6th year students from Wednesday to Friday every week. They experience a few patients and learn how to take a patients' history, physical findings, functional evaluation, and how to plan rehabilitation programs. We have introduced a few of elective students for elective clinical clerkship to our collaborating hospitals with specialized rehabilitation ward.

In addition, we have provided the training of students including physical therapy, occupational therapy, and speech therapy. Twenty students or more come and stay at the university hospital annually as a long-term clerkship from several PT/OT/ST training schools.

Research activities

Our research activities are growing up. In 2006, the Rehabilitation Center moved to the new building and a research laboratory was provided for the first time. As the motion analysis system was partially renewed, we are planning our researches mainly in the field of musculoskeletal disabilities. In addition, we are planning collaborating researches with other departments in our hospital, other faculties in our university, and institutions outside the University of Tokyo. The ongoing projects are as follows.

- 1) 3D Motion analysis of patients with musculoskeletal disorders
- 2) Prognostic evaluation of patients with metastatic bone tumors
- 3) Rehabilitation and long-term outcome in patients with skeletal dysplasias
- 4) Pathology and treatment for patients with congenital limb deficiencies
- 5) Analysis of rehabilitation outcome using DPC data

References

1. Goto M, Haga N, Takedani H: Physical activity and its related factors in Japanese people with haemophilia. *Haemophilia* 25: e267-e273, 2019
2. Mano H, Fujiwara S, Haga N: Body knowledge in children with congenital lower limb deficiency. *Pediatr Int* 61(2): 158-165, 2019
3. Matsushita M, Kitoh H, Mishima K, Yamashita S, Haga N, Fujiwara S, Ozono K, Kubota T, Kitaoka T, Ishiguro N: Physical, mental and social problems of adolescent and adult patients with achondroplasia. *Calc Tissue Int* 104(4): 364-372, 2019
4. Nakahara Y, Kitoh H, Nakashima Y, Toguchida J, Haga N: The longitudinal study of activities of daily living and quality of life in Japanese patients with fibrodysplasia ossificans progressiva. *Disabil Rehabil* 41(6): 699-704, 2019
5. Taya M, Amiya E*, Hatano M, Maki H, Hosoya Y, Ishida J, Bujo C, Tsuji M, Konishi Y, Yokota K, Haga N, Komuro I: Inspiratory muscle training for advanced heart failure with lamin-related muscular dystrophy. *J Cardiol Cases* 2019, jccase 20(6): 232-234, 2019.9
6. Yamoto K, Saitsu H, Nishimura G, Kosaki R, Takayama S, Haga N, Tonoki H, Okumura A, Horii E, Okamoto N, Suzumura H, Ikegawa S, Kato F, Fujisawa Y, Nagata E, Takada S, Fukami M, Ogata T: Comprehensive clinical and molecular studies in split hand/foot malformation: identification of two plausible candidate genes (LRP6 and UBA2). *Eur J Hum Genet* 27: 1845-1857, 2019
7. Yoshida M, Matsunaga A, Igawa Y, Fujimura T, Shinoda Y, Aizawa N, Sato Y, Kamei J, Kume H, Homma Y, Haga N, Sanada H*: May preoperative ultrasound-guided pelvic floor muscle training promote early recovery of urinary continence after robot-assisted radical prostatectomy? *Neurourol Urodyn* 38(1): 158-164, 2019
8. Ogura K, Uehara K, Akiyama T, Shinoda Y, Iwata S, Tsukushi S, Kobayashi E, Hirose T, Yonemoto T, Endo M, Tanzawa Y, Nakatani F, Kawano H, Tanaka S, Kawai A: Development of a patient-oriented disease specific outcome measure of health-related quality of life (HRQOL) for

- musculoskeletal oncology patients. *J Orthop Sci* 24(3): 539-547, 2019
9. Fujimura T, Igawa Y, Aizawa N, Niimi A, Yamada Y, Sugihara T, Kamei J, Sato Y, Matsunaga A, Yoshida M, Shinoda Y, Fukuhara H, Nakagawa T, Homma Y, Kume H: Longitudinal change of comprehensive lower urinary tract symptoms and various types of urinary incontinence during robot-assisted radical prostatectomy. *Neurourol Urodyn* 38(4): 1067-1075, 2019
 10. Shinoda Y, Sawada R, Yoshikawa F, Oki T, Hirai T, Kobayashi H, Matsudaira K, Oka H, Tanaka S, Kawano H, Haga N: Factors related to the quality of life in patients with bone metastases. *Clin Exp Metastasis* 36(5): 441-448, 2019
 11. Shinoda Y, Kobayashi H, Kaneko M, Ohashi S, Bessho M, Hayashi N, Oka H, Imanishi J, Sawada R, Ogura K, Tanaka S, Haga N, Kawano H: Prediction of the pathological fracture risk during stance and fall-loading configurations for metastases in the proximal femur, using a computed tomography-based finite element method. *J Orthop Sci* 24(6): 1074-1080, 2019
 12. Morita K, Miura K, Fujimoto M, Yamamori H, Yasuda Y, Kudo N, Azechi H, Okada N, Koshiyama D, Shiino T, Fukunaga M, Watanabe Y, Ikeda M, Kasai K, Hashimoto R: Eye - movement characteristics of schizophrenia and their association with cortical thickness. *Psychiatry Clin. Neurosci.* 73: 508–9, 2019
 13. Morita K, Miura K, Kasai K, Hashimoto R: Eye movement characteristics in schizophrenia: A recent update with clinical implications. *Neuropsychopharmacol Rep.* Epub ahead of print, 2019
 14. Morita K, Miura K, Fujimoto M, Yamamori H, Yasuda Y, Kudo N, Azechi H, Okada N, Koshiyama D, Ikeda M, Kasai K, Hashimoto R: Eye movement abnormalities and their association with cognitive impairments in schizophrenia. *Schizophr. Res.* 209: 255–62, 2019

Surgical Sciences

3. Vital Care Medicine

Department of Anesthesiology

Professor

Kanji Uchida, M.D., Ph.D.

Associate Professor

Masahiko Sumitani, M.D., Ph.D.

Project Associate Professor

Maiko Hasegawa, M.D., Ph.D.

Lecturer

Nobuko Ito, M.D., Ph.D., Masahiko Bougaki, M.D., Ph.D.,
Gaku Kawamura, M.D., Ph.D., Taro Kariya, M.D., Ph.D.,
Masaaki Asamoto, M.D., Ph.D., Michiko Ushio, M.D., Reo Inoue, M.D., Ph.D.

Project Lecturer

Takuma Hiraiwa, M.D., Ayako Hirai, M.D.

Associate

Yosuke Imai, M.D., Ph.D., Ken Kuwajima, M.D., Ph.D., Yuho Tamai, M.D.,
Yoko Hoshino, M.D., Ph.D., Kazuhito Mietani, M.D., Ph.D.,
Yuko Araki, M.D., Takamitsu Ikeda, M.D., Ph.D., Ai Furuta, M.D.,
Masaki Iwakiri, M.D., Mariko Ezaka, M.D., Yuji Ueda, M.D., Miyako Nagaya, M.D.,
Tomoaki Nakamura, M.D., Yoshika Sudo, M.D., Kento Omi, M.D.,
Junko Tsukamoto, M.D., Yuki Odawara, M.D., Kaoru Kato, M.D.,
Gen Kawashima, M.D., Chiharu Kushida, M.D., Akio Kishikawa, M.D.,
Yaeko Yokoshima, M.D.

Homepage <https://www.ut-anes.org/>

Introduction and Organization

The Department of Anesthesiology was established in 1952 and is the oldest department of anesthesiology in Japan. As of March 1, 2023, the Department of Anesthesiology consists of Professor Kanji Uchida; Associate Professor Masahiko Sumitani; Project Associate Professor Maiko Hasegawa; Lecturers Nobuko Ito, Masahiko Bougaki, Gaku Kawamura, Taro Kariya, Masaaki Asamoto, Michiko Ushio, Reo Inoue; Project Lecturer Takuma Hiraiwa, Ayako Hirai;

22 Associates, 13 anesthesiology residents, and 8 graduate students. The outpatient clinic is located on the 2nd floor of Outpatient Clinic Building and the 3rd floor of Central Clinical Service Building 2, the inpatient units are located on the 9th floor south of Inpatient Building A, and the offices and laboratories are located on Clinical Research Building East, Central Building South, and the 4th floor of Clinical Research Building A. The current activities of our department in clinic, education, and research are

described below.

Clinical activities

Department of Anesthesiology is in charge of anesthesia and perioperative management for patients undergoing surgery, acute and chronic pain treatment, and palliative care for cancer patients, of the University of Tokyo Hospital. The number of surgeries at the University of Tokyo Hospital increased as a result of the doubling of the number of operating rooms to 23 when the Central Clinical Service Building 2 became operational in January 2007, and the annual number of surgical cases reached 11,323 (8,831 managed by the anesthesiologists) in FY2019. In FY2020, the number of cases decreased due to the impact of the COVID-19 pandemic. However, from FY2021, there has been a recovery trend, and in FY2023 (Apr 2023 – Mar 2024), the total number of surgeries reached 11,871 cases, with 8,535 cases managed by the anesthesiologists, exceeding the pre-COVID levels. The number of surgeries for patients with many complications and elderly patients has been increasing every year, and in addition, heart, liver, and lung transplants from brain-dead donors have been performed.

Because many patients with severe and complicated conditions, both surgically and medically, are treated at the University of Tokyo Hospital, we routinely provide anesthesia for patients with many preoperative comorbidities, including transplant recipients with end-stage organ failure. We contribute to a good postoperative recovery by performing a careful preoperative assessment, optimizing the patient's condition preoperatively, and performing appropriate intraoperative anesthetic management. In the operating rooms, we are also well-prepared to respond quickly to medical or surgical emergencies that may occur during surgery.

For preoperative patients, we provide outpatient and inpatient preoperative consultation service every weekday for more detailed preoperative evaluation for complicated cases, and took care of 1,378 preoperative patients in FY2022. We have actively engaged in the Perioperative Management Center Program and are designing and implementing a system for more efficient and appropriate

perioperative patient management. Starting from FY2022, we significantly expanded the preoperative evaluations by anesthesiologists in the outpatient basis. This expansion includes 4,810 outpatient preoperative evaluation visits (in addition to 193 consultations for oral care) and 1,099 evaluations for inpatients, all conducted in the outpatient booths, which marks a significant shift from predominantly conducting preoperative evaluations on the inpatient wards. As for postoperative care, we are in charge of postoperative intensive patient care in the ICU2 in cooperation with the Department of Acute Medicine, contributing to safe postoperative management and recovery. The number of postoperative intensive care patients taken care of by the staff members of our department was 1,119 in FY2022.

We have also established an obstetric anesthesia team to improve the safety and comfort of perinatal care. The obstetric anesthesia outpatient clinic is opened once or twice a week to evaluate the anesthetic risk of pregnant women, and the number of visitors in FY2022 was 315. The number of neuraxial labor analgesia was 321 in FY2022.

As an outpatient clinic, the Pain Relief Center (Pain Clinic) is open every weekday. For patients with various pain disorders (including those hospitalized in other departments), we focus on not only the sensory factors of pain but also the biopsychosocial factors, and conduct multidisciplinary pain evaluation and treatment, including neurological, neuropsychiatric and psychiatric evaluations, in cooperation with multiple departments. The number of outpatients in FY2022 was 4,994, of which 258 were first-time patients. The number of active beds was 1, and the number of inpatients was 11. There were 137 requests for pain consultation for inpatients in FY2022.

In close collaboration with our department, the Department of Pain and Palliative Medicine provides multidisciplinary palliative care by the palliative care team, and is also in charge of the outpatient cancer treatment pain clinic for chronic pain associated with cancer treatment and the second opinion clinic for cancer pain in the supportive care phase to the advanced stage, in accordance with the characteristics of the University of Tokyo Hospital as a cancer treatment institution.

Education

We give lectures for fourth-year medical students and provide clinical education (Clinical Clerkship) for fifth and sixth-year medical students on a person-to-person basis with our faculty staff members. The lectures of the FY2023 were: History and mechanisms of anesthesia, Inhalational anesthesia, Intravenous anesthesia, Regional and local anesthesia, Preoperative evaluation, Management of the cardiovascular system in anesthesia, Intraoperative monitoring, Airway management in anesthesia, Postoperative management, and Pain clinic.

The major content of the Clinical Clerkship consists of (1) surgical anesthesia clerkship, (2) pain clinic clerkship, and (3) short lectures. In the surgical anesthesia clerkship, students participate in preoperative examinations, planning of anesthesia management, and onsite anesthesia management to learn the basic knowledge of examination and testing techniques as well as physiology and pharmacology necessary for perioperative management in a clinical setting. Pain clinic clerkship aims to deepen understanding of the causes of various intractable pains and therapeutic methods focusing on pharmacotherapy, nerve block therapy, exercise therapy, and cognitive-behavioral therapy. The short lectures cover seven topics: General anesthesiology, Airway maintenance and intubation, Central venous access placement, Subarachnoid spinal anesthesia, Peripheral nerve block, Postoperative ICU management, and Pain clinic. Practical training using a simulator is also provided for tracheal intubation, central venous puncture, and subarachnoid spinal anesthesia. As a summary of the Clinical Clerkship education, we ask the students to submit reports on anesthesia cases and reports on anesthetics and cardiovascular drugs, with presentations and discussions on the contents.

For post-graduate education, we accepted a total of 111 junior residents of PGY1 and 2 from the General Education Center as rotators (1-2 months for each rotator) in FY2022. The training includes anesthesia management, preoperative and intraoperative management, and basic skills and knowledge in emergency and resuscitation settings. For the 11 anesthesiology residents of PGY3+, faculty staffs

teach and supervise daily clinical anesthesia, postoperative ICU care, obstetric anesthesia, and pain clinic. The anesthesiology residents are encouraged to give presentations at scientific meetings, including the Japanese Society of Anesthesiologists (JSA) annual meetings, and publish papers. Anesthesiology residents achieve JSA board certification by the end of the training. In addition, journal clubs and case studies are organized to cultivate a professional attitude in residents and develop their competency to perform care and research as independent anesthesiologists.

Research

Our department has seven research groups. The research fields include respiratory, cardiovascular, pain, nervous, and immune systems.

Our ongoing and recent major research subjects are:

- A role of cytokine signaling in acute lung injury;
- Transpulmonary pressure during mechanical ventilation;
- Exploring risk factors of perioperative exacerbation of interstitial lung disease;
- Modification of immune system by anesthesia;
- Apoptotic signal transduction induced by sepsis or ischemia-reperfusion injury;
- A role of lipid mediators in the formation of hyperalgesia;
- A role of spinal microglial cells in the development of inflammation-mediated neuropathic pain;
- Cognitive-behavioral therapy on chronic pain;
- Analysis of electroencephalography during general anesthesia;
- Exploring relationship between postoperative delirium and blood-brain barrier dysfunction;
- Clinical significance of fatty acid metabolites in general anesthesia;
- Retrospective analyses on perioperative management of left ventricular assisting device implantation or heart transplantation;
- Physiology and molecular biology of left/right heart failure of animal models;
- Invention and validation of new anesthetic procedures with emerging technologies;

- Epidemiological survey and outcome study with large administrative database.

conditions: Clinical observation study. *Int J Mol Sci.* 2023;24(8):6986.

Publications

1. Bougaki M, Uchida K. Is meningocele an absolute contraindication for epidural labor analgesia? *JA Clin Rep.* 2023;9:74.
2. Kasahara S, Kanda S, Takahashi M, Fujioka M, Morita T, Matsudaira K, Sato N, Hattori M, Momose T, Niwa S-I, Uchida K. Case report: Guanfacine and methylphenidate improved chronic lower back pain in autosomal dominant polycystic kidney disease with comorbid attention deficit hyperactivity disorder and autism spectrum disorder. *Front Pediatr.* 2023;11:1283823.
3. Kasahara S, Kato Y, Takahashi K, Matsudaira K, Sato N, Fukuda KI, Toyofuku A, Niwa SI, Uchida K. Improvement in persistent idiopathic facial pain with comorbid ADHD using the combination of a dopamine system stabilizer and psychostimulant: A case report. *Clin Case Rep.* 2023;11(6):e7552.
4. Kasahara S, Kato Y, Takahashi M, Matsudaira K, Sato N, Niwa S-I, Momose T, Uchida K. Case report: Remission of chronic low back pain and oral dysesthesia comorbid with attention deficit/hyperactivity disorder by treatment with atomoxetine and pramipexole. *Front Pain Res (Lausanne).* 2023;4:1159134.
5. Kasahara S, Takahashi M, Morita T, Matsudaira K, Sato N, Momose T, Niwa S-I, Uchida K. Case report: Atomoxetine improves chronic pain with comorbid post-traumatic stress disorder and attention deficit hyperactivity disorder. *Front Psychiatry.* 2023;14:1221694.
6. Seto F, Kawamura G, Hosoki K, Ushio M, Jo T, Uchida K. Secondary analysis of preoperative predictors for acute postoperative exacerbation in interstitial lung disease. *Sci Rep.* 2023;13(1):13955.
7. Tsuchida R, Nishizawa D, Fukuda K-I, Ichinohe T, Kano K, Kurano M, Ikeda K, Sumitani M. Genetic polymorphisms of *ENPP2* are possibly associated with pain severity and opioid dose requirements in patients with inflammatory pain

Department of Emergency and Critical Care Medicine

Professor

Kent Doi, M.D.

Associate Professor

Takehiro Matsubara, M.D.

Project Lecturer

Miyuki Yamamoto, M.D.

Research Associate

Tomoki Wada, M. D., Ryohei Horie, M. D., Toshifumi Asada, M.D., Hitomi Nakamura, M.D.
Jinsuke Mizuno, M.D., Mitsuhiro Tokuda, M.D., Yuko Sato, M.D. Mami Kiriya, M.D.
Naohiro Takahashi, M.D.

Project Research Associate

Mio Shikama, M.D.

Homepage <http://uteccm.umin.jp/>

Introduction and Organization

Department of Emergency and Critical Care Medicine was established in 1965, as the emergency service within the Central Clinical Service Facilities of the University of Tokyo Hospital and at the same time as the intensive care service for in-hospital patients, it became a tertiary emergency care and critical care center in the metropolitan Tokyo and also became the principal teaching facility of the University of Tokyo. It is a designated Level I Trauma Center, and also the home of one of the newest Life Flight aeromedical services in the country.

The Emergency Center sees approximately 17,000 patients per year. It contains major trauma and cardiac resuscitation rooms complete with STAT X-ray and full monitoring and resuscitation equipment. There are 9 treatment spaces including space for orthopedics, gynecology, and Ophthalmology-ENT evaluations. 10 overnight-stay monitored beds, X-ray, rapid spiral

CT, ultrasound, angiography and STAT Lab are located adjacent to the Emergency Center.

In September, 2001, the University of Tokyo Hospital opened the In-patient Ward A and our department has necessarily extended services for management of critical patients, in the new Critical Care Center now containing adult ICU/CCU of 16 beds in ICU1, 18 beds in ICU2 and 6 beds in Emergency ICU.

The Emergency Care Center and the Critical Care Center see an excellent mix of multiple trauma, high-acuity medical, surgical, pediatric, and gynecologic patients. The Life Flight service provides another opportunity for exposure to critically ill patients. Consult services are available from all of the clinical departments of the Medical School. The university of Tokyo hospital was officially designated as emergency medical care center in December 2010.

Clinical activities

Our clinical activities are divided into three categories as follows:

1) Emergency medicine

Our department is responsible for not only tertiary emergency but also primary and secondary emergency care on 24-hour-a-day basis.

The new ER, four times the size of the previous ER was built in November, 2006. The facility has 5 consultation rooms, 4 specialized consultation rooms for dentistry, ophthalmology, otorhinolaryngology and gynecology, 3 resuscitation bays, and 4 observation beds.

2) Intensive care

Staff members specialized in internal medicine, cardiovascular medicine, orthopedic surgery, surgery, neurosurgery or anesthesiology create “the semi-closed ICU” model. We are responsible for the entire care of the critically ill patients (i.e. patients with respiratory insufficiency such as ARDS, acute kidney injury, sepsis, MOF, shock), post-operative patients, and tertiary emergency patients, placing an emphasis on evidence-based medical therapy.

3) Risk management

It is split into two categories – in-hospital and out of hospital disasters. In regard to in-hospital risk management, including “code blue emergency”, we are responsible for patient safety on 24-hour/365-day basis. And in regard to out of hospital risk management, our hospital has been authorized by the Tokyo Metropolitan Government as a disaster base hospital, and also the Government has requested the formation of Disaster Medical Assistant Team (DMAT). We have oxygen and medical suction equipment on the passageways in the ER in case of treating the large number of disaster patients.

Teaching activities

In the systematic lectures of M2, the latest findings related to the field of emergency medicine, such as general emergency medicine, basics of initial emergency care, cardiopulmonary resuscitation, initial trauma care, and disaster medicine, are lectured and introduced.

In M3, students are in charge of general medicine

and participate in actual practice of emergency general medicine in the emergency department, and in M4, students practice emergency and intensive care medicine and receive lectures on disaster medicine in addition to practical training on critical care in the intensive care unit.

Since 2004, post-graduate clinical training has become mandatory and all residents are required to receive training in the emergency department. In accordance with the training guidelines of the Ministry of Health, Labour and Welfare, residents learn and practice comprehensive emergency medicine that covers primary to tertiary care in the emergency department. In addition, initial clinical trainees are also assigned to the intensive care unit, where they are educated to understand intensive care from the viewpoint of pathophysiology and internal medicine.

In 2006, we started the second semester of clinical training, and are educating the residents in applied crisis medicine such as initial trauma care, cardiopulmonary resuscitation, multiple organ failure, shock, and mechanical assistance for various organ failures, etc.

Research activities

Our clinical studies revealed that organ network disruption could be observed by network analysis with clinical parameters and new biomarkers of ICU patients.

References

1. Sato Y, Inokuchi R, Yamamoto M, Horie R, Asada T, Matsubara T, Doi K. Impact of renal dysfunction on the diagnosis of acute pancreatitis using urinary trypsinogen-2: A retrospective study. *Nephrology (Carlton)*. 2024 Jun;29(6):338-343.
2. Kameda S, Maeda A, Maeda S, Inoue Y, Takahashi K, Kageyama A, Doi K, Fujii T. Dose of nafamostat mesylate during continuous kidney replacement therapy in critically ill patients: a two-centre observational study. *BMC Nephrol*. 2024 Feb 26;25(1):69.
3. Ohbe H, Sasabuchi Y, Doi K, Matsui H, Yasunaga H. The authors reply. *Crit Care Med*. 2024 Feb 1;52(2):e108-e109.
4. Arashiro T, Miwa M, Nakagawa H, Takamatsu J, Oba K, Fujimi S, Kikuchi H, Iwasawa T, Kanbe F,

Oyama K, Kanai M, Ogata Y, Asakura T, Asami T, Mizuno K, Sugita M, Jinta T, Nishida Y, Kato H, Atagi K, Higaki T, Nakano Y, Tsutsumi T, Doi K, Okugawa S, Ueda A, Nakamura A, Yoshida T, Shimada-Sammori K, Shimizu K, Fujita Y, Okochi Y, Tochitani K, Nakanishi A, Rinka H, Taniyama D, Yamaguchi A, Uchikura T, Matsunaga M, Aono H, Hamaguchi M, Motoda K, Nakayama S, Yamamoto K, Oka H, Tanaka K, Inoue T, Kobayashi M, Fujitani S, Tsukahara M, Takeda S, Stucky A, Suzuki T, Smith C, Hibberd M, Ariyoshi K, Fujino Y, Arima Y, Takeda S, Hashimoto S, Suzuki M. COVID-19 vaccine effectiveness against severe COVID-19 requiring oxygen therapy, invasive mechanical ventilation, and death in Japan: A multicenter case-control study (MOTIVATE study). *Vaccine*. 2024 Jan 25; 42(3):677-688.

5. Hayase N, Yamamoto M, Asada T, Isshiki R, Doi K. Tachycardia and Acute Kidney Injury among Critically Ill Patients with Sepsis: A Prospective Observational Study. *Blood Purif*. 2024;53(8): 641-649.
6. Pickkers P, Angus DC, Bass K, Bellomo R, van den Berg E, Bernholz J, Bestle MH, Doi K, Doig CJ, Ferrer R, Francois B, Gammelager H, Pedersen UG, Hoste E, Iversen S, Joannidis M, Kellum JA, Liu K, Meersch M, Mehta R, Millington S, Murray PT, Nichol A, Ostermann M, Pettilä V, Solling C, Winkel M, Young PJ, Zarbock A; REVIVAL investigators. Phase-3 trial of recombinant human alkaline phosphatase for patients with sepsis-associated acute kidney injury (REVIVAL). *Intensive Care Med*. 2024 Jan;50(1): 68-78.

Health Sciences and Nursing

1. Health Sciences

Department of Mental Health

Professor

Daisuke Nishi, M.D., Ph.D.

Lecturer

Natsu Sasaki, M.D., Ph.D.

Homepage <https://mhpn.m.u-tokyo.ac.jp/>

Introduction and Organization

The department was firstly established as Department of Fourth Clinical Medical Nursing in School of Health Care and Nursing in 1957. When the School of Health Care and Nursing was reorganized as the School of Health Sciences in 1965, the department was renamed Department of Mental Health. In 1992, as School of Health Sciences became The School of Health Science and Nursing, Department of Mental Health became Department of Mental Health and Psychiatric Nursing. As the result of the shift to the chair system of the Graduate School of Medicine in 1996, two departments were established, Department of Mental Health and Department of Psychiatric Nursing. Faculty, staff, and students of two departments have been working cooperatively ever since. Since 2007, Department of Mental Health became a part of School of Public Health, with a perspective of “public mental health.”

At present, the Department of Mental Health is made up of professors, lecturers, part-time lecturers, visiting researchers and graduate students.

The department has two major objectives: one is to teach mental health to undergraduate and graduate students in order to produce global leaders in research and practice in this field. The other is to conduct cutting-edge research in the fields of mental health.

All of the activities of the department are conducted in collaboration with staff members in the departments, other departments within the University of Tokyo, and institutions within and outside Japan.

Teaching activities

The department is responsible for giving lectures on mental health; mental disorders; clinical and health psychology; and psychometry and behavior evaluation to undergraduate students. Other than lectures, the department provides students opportunities to experience mental health activities in relevant mental health settings.

The department provides graduate courses on mental health I and II, featuring epidemiology and practice in mental health and occupational mental health, respectively. The department also provided a 1.5 hour seminar every Wednesday evening for 20 weeks in each semester (40 weeks per year) for graduate students and research students, with presentations of research plans and progress, and literature review by graduate students, as well as presentation of and lectures by guest speakers.

Research activities

The department conducts research on mental health epidemiology, perinatal mental health, traumatic stress and resilience, and mental health in the workplace. In the field of mental health epidemiology, we are in charge of the survey in Japan of a large-scale international collaborative study (the World Mental Health Survey), which is being conducted under the initiative of Harvard University. In perinatal mental health, we are working with companies to prevent perinatal depression. For traumatic stress, we are working to evaluate the effectiveness of trauma-informed care and to promote its implementation. For

mental health in the workplace, we are developing programs to prevent depression in the workforce. In addition, we are working on suicide prevention, disaster mental health, and international mental health in collaboration with researchers from domestic and international institutions and universities. Many of these studies are conducted in collaboration with researchers from domestic and international institutions and universities.

References

1. Sasaki N, Nishi D. Euthymia scale as a protective factor for depressive symptoms: a one-year follow-up longitudinal study. *BMC Res Notes*. 2023 Sep 22;16(1):230.
2. Obikane E, Nishi D, Morisaki N, Tabuchi T. Risk factors of paternal perinatal depression during the COVID-19 pandemic in Japan. *J Psychosom Obstet Gynaecol*. 2023 Dec;44(1):2245556.
3. Nakayama R, Nishi D, Sato M, Ito A, Uchiyama K, Higuchi Y, Takahashi H, Ohinata K. The Effect of the Rice Endosperm Protein Hydrolysate on the Subjective Negative Mood Status in Healthy Humans: A Randomized, Double-Blind, and Placebo-Controlled Clinical Trial. *Nutrients*. 2023 Aug 7;15(15):3491.
4. Sasaki N, Imamura K, Nishi D, Watanabe K, Asaoka H, Sekiya Y, Tsuno K, Kobayashi Y, Obikane E, Kawakami N. The effect of internet-based acceptance and commitment therapy (iACT) on psychological well-being among working women with a pre-school child: A randomized controlled trial. *Journal of Contextual Behavioral Science*. 2023 Apr ;28:33-47.
5. Sasaki N, Tabuchi T, Okubo R, Nishi D. Association of living condition using urbanisation level and neighbourhood deprivation with loneliness and social isolation during COVID-19 pandemic: a cross-sectional study of the nationwide data in Japan. *BMJ Public Health*. 2023 Nov 28;1(1):e000341.
6. Sasaki N, Tabuchi T, Fujiwara T, Nishi D. Adverse childhood experiences and living in the socially deprived areas in adulthood: a cross-sectional study of the nationwide data in Japan. *BMC Public Health*. 2023 Aug 24;23(1):1616.
7. Sasaki N, Kuroda R, Mikami Y, Tsuno K, Imamura K, Nishi D, Kawakami N. Working environment at home and mental health in employees working from home in Japan during COVID-19 pandemic: A cross-sectional study. *J Occup Health*. 2023 Jan-Dec;65(1): e12410.
8. Fukasawa M, Nishi D, Umeda M, Akiyama T, Horikoshi N, Yasumura S, Yabe H, Suzuki Y, Bromet EJ, Kawakami N. Effects of disaster-related traumatic events on worry about radiation and COVID-19: A decade after the Fukushima nuclear power plant accident. *J Psychiatr Res*. 2023 Jul; 163:135-141.
9. Kataoka M, Kotake R, Asaoka H, Miyamoto Y, Nishi D. Research note reliability and validity of Japanese version of the trauma-informed care provider survey (TIC provider survey). *BMC Res Notes*. 2023 May 2;16(1):68.
10. Arakawa Y, Haseda M, Inoue K, Nishioka D, Kino S, Nishi D, Hashimoto H, Kondo N. Effectiveness of mHealth consultation services for preventing postpartum depressive symptoms: a randomized clinical trial. *BMC Med*. 2023 Jun 26; 21(1):221.
11. Asaoka H, Koido Y, Kawashima Y, Ikeda M, Miyamoto Y, Nishi D. Association Between Attitudes Toward Trauma Informed Care and Psychological First-Aid Training Experience Among Health Care Professionals in Japan. *Disaster Med Public Health Prep*. 2023 Aug 3;17: e443.
12. Hazumi M, Kataoka M, Usuda K, Narita Z, Okazaki E, Nishi D. Difference in the risk of discrimination on psychological distress experienced by early wave infected and late wave infected COVID-19 survivors in Japan. *Sci Rep*. 2023 Aug 12;13(1):13139.
13. McGrath JJ, Al-Hamzawi A, Alonso J, Altwaijri Y, Andrade LH, Bromet EJ, Bruffaerts R, de Almeida JMC, Chardoul S, Chiu WT, Degenhardt L, Demler OV, Ferry F, Gureje O, Haro JM, Karam EG, Karam G, Khaled SM, Kovess-Masfety V, Magno M, Medina-Mora ME, Moskalewicz J, Navarro-Mateu F, Nishi D, Plana-Ripoll O, Posada-Villa J, Rapsey C,

- Sampson NA, Stagnaro JC, Stein DJ, Ten Have M, Torres Y, Vladescu C, Woodruff PW, Zarkov Z, Kessler RC; WHO World Mental Health Survey Collaborators. Age of onset and cumulative risk of mental disorders: a cross-national analysis of population surveys from 29 countries. *Lancet Psychiatry*. 2023 Sep;10(9):668-681.
14. Kanamori Y, Miyamoto Y, Sawada U, Iida M, Tabuchi T, Nishi D. Association between adverse childhood experience and unintended pregnancy among Japanese women: a large-scale cross-sectional study. *J Psychosom Obstet Gynaecol*. 2023 Dec;44(1):2274295.
 15. Asaoka H, Sasaki N, Koido Y, Kawashima Y, Ikeda M, Miyamoto Y, Nishi D. Reliability and validity of the Japanese version of the Professional Fulfillment Index among healthcare professionals: A validation study. *J Occup Health*. 2023 Jan-Dec;65(1): e12422. Iida M, Sakuraya A, Imamura K, Asaoka H, Arima H, Ando E, Inoue A, Inoue R, Iwanaga M, Eguchi H, Otsuka Y, Kobayashi Y, Komase Y, Kuribayashi K, Sasaki N, Tsuno K, Hino A, Watanabe K, Ebara T, Shimazu A, Kawakami N, Tsutsumi A. Effects of participatory organizational interventions on mental health and work performance: A protocol for systematic review and meta-analysis. *Journal of Occupational Health*. 2023:uia028.
 16. Dohi Y, Imamura K, Sasaki N, Komase Y, Sakuraya A, Nakamura Y, Maejima M, Aoyama M, Kawakami N, Miyamoto Y. (2023). Effects of an internet-delivered behavioral activation program on improving work engagement among Japanese workers: A pre-and post-test study. *J Occup Environ Med*. 65 (10)
 17. Eguchi H, Watanabe K, Kawakami N, Ando E, Imamura K, Sakuraya A, Sasaki N, Inoue A, Tsuno K, Otsuka Y, Inoue R, Nishida N, Iwanaga M, Hino A, Shimazu A, Tsutsumi A. Work-related psychosocial factors and inflammatory markers: A systematic review and meta-analysis. *Journal of psychosomatic research*. 2023;170: 111349.
 18. Iwanaga M, Iida M, Sasaki N, Kotake R, Morita Y, Asaoka H, Nozawa K, Iwanaga H, Kawakami N. Association between school bullying experience and work-related subjective well-being: A systematic review. *Environmental and Occupational Health Practice*. 2023.
 19. Kawakami N, Sasaki N, Asaoka H, Kuroda R, Tsuno K, Imamura K. Effects of workplace measures against COVID-19 and employees' worry about them on the onset of major depressive episodes: A 13-month prospective study of full-time employees. *Journal of affective disorders*. 2023;322:187-93.
 20. Watanabe K, Imamura K, Eguchi H, Hidaka Y, Komase Y, Sakuraya A, Inoue A, Kobayashi Y, Sasaki N, Tsuno K, Ando E, Arima H, Asaoka H, Hino A, Iida M, Iwanaga M, Inoue R, Otsuka Y, Shimazu A, Kawakami N, Tsutsumi A. Usage of the Brief Job Stress Questionnaire: A Systematic Review of a Comprehensive Job Stress Questionnaire in Japan from 2003 to 2021. *International Journal of Environmental Research and Public Health*. 2023; 20(3):1814.
 21. Sakuraya A, Iida M, Imamura K, Ando E, Arima H, Asaoka H, Eguchi H, Hidaka Y, Hino A, Inoue A, Inoue R, Iwanaga M, Kobayashi Y, Komase Y, Otsuka Y, Sasaki N, Shimazu A, Tsuno K, Watanabe K, Kawakami N, Tsutsumi A. A proposed definition of participatory organizational interventions. *Journal of occupational health*. 2023;65(1):e12386.
 22. Iida M, Sawada U (equal contribution), Usuda K, Hazumi M, Okazaki E, Ogura K, Kataoka M, Sasaki N, Ojio Y, Matsunaga A, Umemoto I, Makino M, Nakashita A, Kamikawa C, Kuroda N, Kuga H, Fujii C & Nishi D. Effects of the Mental Health Supporter Training Program on mental health-related public stigma among Japanese people: A pretest/posttest study. *Psychiatry and Clinical Neurosciences Reports*, 2024 Mar 15; 3(1), e176.
 23. Czepiel D, McCormack C, da Silva ATC, Seblova D, Moro MF, Restrepo-Henao A, Martínez AM, Afolabi O, Alnasser L, Alvarado R, Asaoka H, Ayinde O, Balalian A, Ballester D, Barathie JAL, Basagoitia A, Basic D, Burrone MS, Carta MG, Durand-Arias S, Eskin M, Fernández-Jiménez E, Frey MIF, Gureje O, Isahakyan A, Jaldo R, Karam EG, Khattech D, Lindert J, Martínez-Alés G, Mascayano F, Mediavilla R, Narvaez

Gonzalez JA, Nasser-Karam A, Nishi D, Olaopa O, Ouali U, Puac-Polanco V, Ramírez DE, Ramírez J, Rivera-Segarra E, Rutten BPF, Santaella-Tenorio J, Sapag JC, Šeblová J, Soto MTS, Tavares-Cavalcanti M, Valeri L, Sijbrandij M, Susser ES, Hoek HW, van der Ven E. Inequality on the frontline: A multi-country study on gender differences in mental health among healthcare workers during the COVID-19 pandemic. *Glob Ment Health (Camb)*. 2024 Mar 4;11:e34.

24. Iida M, Sakuraya A, Watanabe K, Imamura K, Sawada U, Akiyama H, Komase Y, Miyamoto Y & Kawakami N. The association between team job crafting and work engagement among nurses: a prospective cohort study. *BMC psychology*, 2024 Feb 9; 12(1), 66.

Department of Biostatistics/ Epidemiology and Preventive Health Sciences

Professor

Yutaka Matsuyama, Ph.D.

Associate Professor

Koji Oba, Ph.D.

Assistant Professor

Yasuhiro Hagiwara, Ph.D., M.P.H., Yui Yoshida, M.D., Ph.D.

Homepage <https://www.epistat.m.u-tokyo.ac.jp/en/>

Introduction and Organization

The Department of Epidemiology and Biostatistics evolved from the Department of Epidemiology in 1992. Since then, we have been responsible for providing educational courses on methodology of epidemiologic research and biostatistics to undergraduate students. We belong to Graduate School of Medicine as Departments of Biostatistics/ Epidemiology and Preventive Health Sciences, providing education for undergraduate as well as graduate-school students and consultation to clinical researchers.

Unfortunately, education programs for biostatistics and epidemiological methodology are not sufficient in Japanese universities and graduate schools compared to the situation in the US and European countries. Nevertheless, the necessity for collaboration among biostatisticians and clinical researchers/ epidemiologists has been claimed in recent years. Hence, the central missions of our educational courses are devoted to provide students expert knowledge and extensive experience in biostatistics and epidemiology to take part in clinical/ epidemiological research as biostatisticians or methodologists. We do not only focus on practical

aspects on statistical analysis in medical research but also place emphasis on the methodological principles of biostatistics/epidemiology.

Our main research area is the development of methodology for clinical/epidemiological research. Of course, it requires keeping in touch with real clinical/epidemiological problems. So, another indispensable research area is a support for real-world clinical and epidemiological studies including clinical trials. To achieve these requirements simultaneously, a non-profit organization the Japan Clinical Research Support Unit was established in 2001 by the former faculty members in our department. This organization J-CRSU had provided research support and coordination in design, data management, and statistical analysis in many projects inside/outside the university. Our experience in J-CRSU is the basis of our supportive activities for clinical research that we work through today.

Teaching activities

- Undergraduate Courses
 - 1) Epidemiology (2 credits)
 - 2) Biostatistics (2 credits; named “Statistics” in medical doctor course)

- 3) Applied Mathematics (2 credits)
 - 4) Biostatistics Practice (1 credit)
 - 5) Practical Examples in Clinical and Epidemiologic Research (1 credit)
 - 6) Medical Data Analysis, and its Practice (1 credit each)
 - 7) Theoretical Epidemiology (2 credits)
- School of Public Health (Graduate School)
 - 1) Statistical Analysis of Medical Research (2 credits)
 - 2) Practice of Biostatistics (2 credits)
 - 3) Design of Medical Research (2 credits)
 - Doctoral Courses (Graduate School)
 - 1) Biostatistics (4 credits)
 - 2) Epidemiology and Preventive Health Sciences (4 credits)
 - 3) Introduction to Medical Statistics (2 credits; for the School of Medicine)

The faculty of the department had provided lectures in a series of educational courses organized by “The Clinical Bioinformatics Research Unit” in 2002-2007.

Research activities

1. Methodology for designing and analyzing clinical trials:
 - Interim analysis
 - Adaptive designs
 - Multiplicity
 - Data management of large-scale multicenter clinical trials
2. Methodology of Biostatistics and theoretical epidemiology:
 - Analysis of longitudinal (time-to-event and/or repeated measures) data
 - Analysis of missing/incomplete data
 - Causal inference
 - Semiparametric modeling
3. International collaboration of individual-level meta-analysis on gastric cancer
4. Coordination and data analysis of collaborative epidemiological/clinical research:
 - Japan Arteriosclerosis Longitudinal Study

- Japan Diabetes Collaborative Study
 - Chronic Kidney Disease Japan Cohort
5. Validity/reliability studies of QOL questionnaires and other rating scales
 6. Pharmacoeconomic assessment of medical technology

We had been supporting some of the above collaborative clinical/epidemiologic studies, which aims to support investigator- initiated studies and to provide education to researchers and support staffs. Currently, we are officially conducting a consultation for design and analysis of clinical trials assisted by the Clinical Research Promotion Center of the University of Tokyo Hospital.

The University of Tokyo participated in "Support Program for Biostatisticians," an industry-government-academia collaborative project launched by the Japan Agency for Medical Research and Development (AMED) in FY2016, and has been participating in its successor, "Promotion Program for Biostatisticians," since FY2021 (principal investigator: Professor Matsuyama). Both projects are aimed at fostering biostatisticians at clinical research institutes and research centers in Japan, and are designed and implemented for master course and one-year post-graduate education/training programs. Our department is also officially participating in these programs, and will provide more and more educational/practical supports to future biostatisticians on the basis of our rich experience in biostatistical education and support in variety of research.

References

1. Fukuda M, Sakamaki K, Oba K. The net benefit for time-to-event outcome in oncology clinical trials with treatment switching. *Clin Trials*. 2023; 20:670–680.
2. Yokoyama R, Takeuchi Y, Kumamaru H, Matsuyama Y. The utility of the self-controlled study design for pharmacoepidemiological studies without an active comparator medication using a medical information database: An application to assess the risk of varenicline on cardiovascular outcomes. *Pharmacoepidemiol Drug Saf*. 2023;32:1068–1076.

3. Hagiwara Y. Using a sample size calculation framework for clinical prediction models when developing and selecting mapping algorithms based on linear regression. *Med Decis Making*. 2023;43:992–996. (Only main publications)
4. Mayanagi S, Oba K, Aoyama T, Tanaka K, Kanda M, Honda M, Maeda H, Kashiwabara K, Muto M, Sakamoto J, Yamagishi H, Yoshikawa T. Feasibility and Safety of Adjuvant chemotherapy for resected colorectal cancer in patients with renal insufficiency: a pooled analysis of individual patient data from five Japanese large-scale clinical trials. *Anticancer Res*. 2023;43:3089–3095.
5. Aoyama T, Oba K, Honda M, Muto M, Mayanagi S, Maeda H, Kanda M, Kashiwabara K, Sakamoto J, Yoshikawa T. The clinical impacts of postoperative complications after colon cancer surgery for the clinical course of adjuvant treatment and survival. *Int J Clin Oncol*. 2023;28:777–784.
6. Fuyama K, Ogawa M, Mizusawa J, Kanemitsu Y, Fujita S, Kawahara T, Sakamaki K, Oba K. Impact of correlations between prioritized outcomes on the net benefit and its estimate by generalized pairwise comparisons. *Stat Med*. 2023;42:1606–1624.
7. Izumi S, Hagiwara Y, Matsuyama Y, Shiroiwa T, Taira N, Kawahara T, Konomura K, Noto S, Fukuda T, Shimozuma K. Impacts of the preceding cancer-specific health-related quality of life instruments on the responses to the subsequent EQ-5D-5L. *Health Qual Life Outcomes*. 2023;21:3.
8. Matsumoto H, Hagiwara Y, Yamamoto-Mitani N, Igarashi A. A randomized control trial for ReDeSign: A dementia-friendly mobile micro-learning training for store workers in Japan. *Gerontologist*. 2023;63:1300–1310.
9. Hagiwara Y, Shiroiwa T, Taira N, Kawahara T, Konomura K, Noto S, Fukuda T, Shimozuma K. Gradient boosted tree approaches for mapping European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 onto 5-level version of EQ-5D index for patients with cancer. *Value Health*. 2023;26:269–279.

Department of Biomedical Ethics & Department of Health Promotion Sciences

Associate Professor

Yoshiyuki Takimoto, M.D., Ph.D.

Lecturer

Eisuke Nakazawa, Ph.D.

Homepage <http://www.ethps.m.u-tokyo.ac.jp/>

Introduction and Organization

The former Department of Health Administration was established in 1967 and Dr. Tsuneo Tanaka became its first professor in 1974. He devoted himself to the development of the community health care system in Japan and published numerous papers concerning the social theory of health administration and data management systems for community health care. He also contributed to the establishment of the School of Health Sciences. In 1985, Dr. Atsuaki Gunji became the second professor of the department. During Dr. Gunji's tenure, two major research projects were undertaken. One was "The effects of physical activity and inactivity on health." From 1990, a 20-day bed rest human experimental study was conducted every year in the context of an international cooperative research project that was supported by government grants. The other project concerned health care systems, especially health care economics and the quality of hospital care.

In 1996, the Department of Health Administration developed into two departments: the Department of Health Economics and the Department of Health Promotion Sciences. Both were established as departments of the Graduate School of Medicine. In 1998, Dr. Yasuki Kobayashi became the professor of the Department of Health Economics. He conducted research into health care delivery systems in Japan. In

2001, he moved to the Department of Public Health. From 1996 to 2002, Dr. Kiyoshi Kawakubo took charge of the Department of Health Promotion Sciences as the associate professor.

In June 2002, Dr. Akira Akabayashi became professor of the Department of Health Economics. Professor Akabayashi's area of research is biomedical ethics. In April 2003, the Department of Health Economics was restructured and named the Department of Biomedical Ethics. Professor Akabayashi retired in March 2023. From 2007, Dr. Jung Su Lee became the associate professor and took charge of the Department of Health Promotion Sciences. In 2017, Dr. Yoshiyuki Takimoto acceded to the chair of the Department of Health Promotion Sciences. In 2019, the Department of Health Promotion Sciences was consolidated into the Department of Biomedical Ethics.

Staff members of the department include an associate professor, a lecturer, and a technical specialist. All three members, a project research associate, three project researchers, ten lecturers from other organizations, and three visiting researchers contribute to department teaching and research activities.

We have six department graduate students. Four of them are doctoral program students.

In this annual report, the organization and

teaching activities are reviewed followed by an explanation of research activities.

Teaching activities

Our departments highly prioritize the teaching and guidance of graduate students and their research activities. Twenty six bachelor theses, twenty five master theses, and fifteen doctoral dissertations were completed between April 2004 and March 2024. Our department's staff members are also responsible for the following undergraduate and graduate courses.

Undergraduate Courses

Required courses

- 1) Introduction to Biomedical Ethics (Lecture)
- 2) Biomedical Ethics I (2 credits, lecture)
- 3) Theory and Science of Health Behavior (2 credits, lecture)
- 4) Seminar in Public Health Science II (2 credits, seminar)
- 5) First-Year Seminar for Natural Science Students (2 credits, seminar)

Elective courses

- 6) Integrated Lecture of Clinical Medicine (Lecture)
- 7) Integrated Lecture of Clinical Medicine, Biomedical ethics (Lecture)
- 8) Integrated Lecture of Clinical Medicine, Biomedical ethics and Geriatric Medicine (Lecture)
- 9) Social Medicine (Lecture)
- 10) Biomedical Ethics II (2 credits, lecture)
- 11) Clinical Ethics (2 credits, lecture)
- 12) Public Health Ethics (2 credits, lecture)

Graduate Courses

- 1) Biomedical Ethics I
- 2) Biomedical Ethics II

In addition to these courses, the department operates lectures, practical training, and joint seminars for research guidance on a regular basis.

Graduate level courses in Biomedical Ethics focus on the analytical study of ethical theories and on the review of several empirical studies within the field and its related areas.

Research activities

The Department of Biomedical Ethics is interested in the current topics of health care ethics. We are currently conducting studies in the fields of biomedical ethics, research ethics and clinical ethics. Methodology is two-folded—theoretical and empirical. While conducting theoretical research on ethics and philosophy of health care, we also have adopted a descriptive approach.

We have recently established The University of Tokyo Center for Biomedical Ethics and Law (CBEL)—a new interdisciplinary and international education research center aimed to address bioethical issues relevant to Japan and the international community. Our center will form an international network by establishing partnerships with research centers overseas (GABEX: Global Alliance of Biomedical Ethics Centers Project). Through these efforts, we will foster the next generation of bioethics experts in policy-making, research, and clinical medicine who are capable of providing international leadership in the future (<http://www.cbhel.jp/>).

Specific research topics include:

- 1) Study of methods for promoting social consensus on topics related to advanced medical technology
- 2) Study of the function and responsibilities of ethics committees in Japan
- 3) Acceptability of advance directives in Japanese society
- 4) Development of evaluative methods for bio-medical ethics education
- 5) Ethical and psychosocial aspects of living related organ transplantation
- 6) Publication of a medical ethics case book for Japan
- 7) Comparative study of clinical ethics in the Asian region
- 8) Historical analyses for the term “bioethics” in the Japanese context

References

1. Arai N, Yokoyama N, Hara M, Takimoto Y. Perceptions of psychosocial and ethical issues and the psychological characteristics of donors in the clinical setting of living kidney donors: A

- qualitative study. *AJOB Empir Bioeth.* 2024; 15(1):22–32. doi: 10.1080/23294515.2023.2232776.
2. Ibuki T, Ibuki A, Nakazawa E. Possibilities and ethical issues of entrusting nursing tasks to robots and artificial intelligence. *Nursing Ethics.* 2023 Online First. doi: 10.1177/09697330221149094.
3. Maeda S, Kamishiraki E, Murata M, Ishikawa E, Nakazawa E, Akabayashi A. Healthcare ethics education for students: A survey of medical and nursing schools in Japan. *Journal of Patient Safety & Conflict Management.* 2023; 15:20–27.
4. Nagao N., Takimoto Y. Clinical ethics consultation in Japan: What does it mean to have a functioning ethics consultation? *Asian Bioeth Rev.* 2024; 16:15–31. doi: 10.1007/s41649-023-00257-2.
5. Nakazawa E, Shaw MH, Akabayashi A. The ethical acceptability of a recipient's choice of donor in directed and non-directed transplantation: Japanese perspective. *Camb Q Healthc Ethics.* 2023; 32(2):216–221. doi: 10.1017/S0963180122000214.
6. Qian Y, Takimoto Y, Wang L, Yasumura A. Exploring cultural and gender differences in moral judgment: A cross-cultural study based on the CNI model. *Curr Psychol.* May 2023. doi: 10.1007/s12144-023-04662-6. [peer reviewed]
7. Sato H, Takimoto Y. Clinical ethics problems in psychiatry and the need for clinical ethics consultation in Japan: A cross-sectional study. *PCN Rep.* 2023; 2:e86. doi: 10.1002/pcn5.86.
8. Tachibana K, Nakazawa E The consciousness of virtue: uncovering the gaps between educational specialists and the general public in their understanding of virtue in Japan. *Front Psychol.* 2024; 14:1171247. doi: 10.3389/fpsyg.2023.1171247.
9. Takimoto Y, Yasumura A. Verification of the Japanese version of Greene's moral dilemma task's validity and reliability. *Psych.* 2023; 5(1): 224–233. doi: 10.3390/psych5010017.
10. Takimoto Y. Should physicians be permitted to refuse follow-up care to patients who have received an organ transplant through organ trafficking? *Transpl Int.* 2023; 36:11529. doi: 10.3389/ti.2023.11529.
11. Toda S, Nakazawa E. Determinism and social paradoxes of explainable artificial intelligence (XAI). *CBEL Report.* 2023; 5(2):47–58.
12. Udagawa M, Nakazawa E, Akabayashi A. Courses of study for the high-school subject “The Public” and its authorized textbooks. *Journal of Seizon and Life Sciences.* 2023; 33(2):119–136.
13. Watanabe E, Lee JS, Ichinohe S, Nakazawa E. Literature review on health disparities and social capital in Japan. *CBEL Report.* 2023; 5(2):26–46.
14. Nakazawa E, Akabayashi A. Fair distribution of burdens and vulnerable groups with physical distancing during a pandemic. In: Julian Savulescu (ed.), Dominic Wilkinson (ed.) . *Pandemic Ethics: From COVID-19 to Disease X* (online edn, Oxford Academic), doi: 10.1093/oso/9780192871688.001.0001 Oxford University Press, April 2023. Chapter 16, p. 337–356.
15. Takahashi S, Nakazawa E, Ichinohe S, Akabayashi Ar, Akabayashi Ak. Wearable technology for monitoring respiratory rate and SpO2 of COVID-19 patients. doi: 10.9734/bpi/rdmms/v3/18568D. In: Darko Nozic (ed.). *Research Developments in Medicine and Medical Science.* Vol. 3. B P International, March 2023. p. 33–53.
16. Akabayashi A, Nakazawa E. What does it mean to truly empathize with a Patient? An analysis of Japanese cases employing the narrative approach perspective. doi: 10.9734/bpi/cidhr/v2/19446D. In: Ashraf Talaat Youssef (ed.). *Current Innovations in Disease and Health Research,* Vol. 2. B P International, July 2023. p. 42–54.

Health Sciences and Nursing

2. Preventive and Administrative Nursing

Department of Nursing Administration / Advanced Clinical Nursing

Associate Professor

Aya Kitamura, Ph.D., R.N.

Assistant Professor

Ryohei Kida, Ph.D., R.N.

Tamaki Isobe, Ph.D., R.N

Homepage <https://nursing-ad.m.u-tokyo.ac.jp/>

Introduction and Organization

The Department of Nursing Administration/Advanced Clinical Nursing has a history and tradition spanning over 60 years. It was first established in 1954 as the Department of Fundamental Nursing within the School of Health Care and Nursing. The School of Health Care and Nursing initially consisted of two basic medical departments and six nursing departments. However, when it was reorganized as the School of Health Sciences in 1965, the nursing departments were reduced to a single department. This department was renamed the Department of Nursing, and became responsible for most of the nursing education in the school. In 1992, the school was renamed the School of Health Sciences and Nursing, and two new nursing departments were established. As a result, the Department of Nursing reverted to its original name, the Department of Fundamental Nursing. In 1996, as part of the reorganization of the Graduate School of Medicine, the Department of Fundamental Nursing was restructured to include two graduate departments: the Department of Nursing Administration and the Department of Advanced Clinical Nursing. These two departments have continued to operate as a unified entity. Additionally, undergraduate education remains under the responsibility of the Department of Fundamental Nursing, as it has traditionally been.

Teaching activities

Undergraduate Courses

In the undergraduate program at the School of Integrated Health Sciences, our department is responsible for lectures and clinical practicums in the following courses: Introduction to Nursing Science, a required course for second-year students; Theory and Methodology of Nursing I, a required course for the Nursing Science major; Basic Nursing Skills, required course in the third year; and Nursing Administration, a required course in the fourth year. Additionally, Theory and Methodology of Nursing II is offered as an elective course in the fourth year.

Introduction to Nursing Science (1 credit)

In this course, students learn the foundational concepts and functions of nursing, as well as nursing theories, the focus of nursing care, and its practices. The course is conducted through lectures, discussions, and inter-professional education.

Theory and Methodology of Nursing I (2 credits)

This course aims to equip students with the knowledge and skills necessary to understand and provide care for individuals. Through lectures, hands-on practice sessions, and clinical shadowing opportunities as part of their early clinical exposure, students learn the

nursing processes essential for delivering appropriate patient care, including skills to assess patients' needs and create optimal care environments.

Basic Nursing Skills (2 credits)

This course focuses on the basics of health assessment, including physical examination skills and fundamental nursing skills, which are essential to ensure holistic and patient-centered nursing care. Students also learn to implement the nursing process through case-based exercises.

Practicum: Basic Nursing Skills (2 credits)

Under the supervision of instructors, students provide care for inpatients during the practicum. They apply the knowledge and skills acquired through lectures and practice sessions, including building nurse-patient relationships, understanding patients, implementing the nursing process, and utilizing basic nursing techniques in clinical settings.

Nursing Administration (1 credit)

This course introduces students to the roles and responsibilities of nurse administrators and managers, covering topics such as organizational management, staffing, safety management, quality improvement, and healthcare policy. Additionally, foundational knowledge essential for effective nursing administration is provided, including health informatics, career development and lifelong learning, team communication, nursing care delivery systems, budgetary issues such as cost effectiveness. These topics are explored through lectures and discussions.

Practicum: Nursing Administration (1 credit)

Students participate in a nursing administrative practicum in hospitals, where they learn about the roles and responsibilities of various departments and the practical aspects of nursing management. Through discussions with nurse administrators and managers, they develop a managerial perspective in nursing.

Theory and Methodology of Nursing II (2 credits)

In this elective course, students develop the knowledge and perspectives necessary for nursing practice and organizational management by critically reading and discussing scholarly articles related to

fundamental nursing and nursing administration.

Graduate Courses

In the graduate program, our department is responsible for the following courses: Special Lecture in Nursing Administration I and II (2 credits each), Special Lecture in Advanced Clinical Nursing I and II (2 credits each), Practice in Nursing Administration I and II (4 credits each), and Seminar in Nursing Administration I and II (4 credits each). In the 2023 academic year, there were no graduate students enrolled, so none of the courses were offered.

Research activities

Our research scope is broad, encompassing individual nursing care technologies, care-related environment, and the systems and organizations that support the nursing profession. We aim to elucidate the underlying mechanisms and their relationships to patient outcomes, thereby creating technologies and systems that maximize the full potential of nursing.

Areas of Nursing Administration

In the areas of Nursing Administration, we aim to elucidate the complex phenomena surrounding organizations and the workforce from various perspectives. These include research on improving the job-related psychological states of working nurses, studies contributing to nursing policies, and investigation into future career development, all with the goal of fostering a society where the sustainability of nursing organizations can be achieved. Research on the psychological states of nurses focuses on factors and outcomes associated with their intention to continue working, such as organizational commitment, work engagement, and person-job fit. Studies contributing to nursing policies address themes such as support for inactive nurses returning to work, appropriate management of work environments, including working hours, education of nursing managers and its outcomes, and the clinical implementation of evidence-based practice. In the area of future career development, we conduct research on employability among nurses.

Areas of Advanced Clinical Nursing

In the areas of Advanced Clinical Nursing, our research focuses on developing innovative nursing techniques by visualizing nursing procedures and elucidating the underlying mechanisms that inform care practices. Specifically, we utilize tools such as ultrasound, thermography, and pressure sensors to assess the effects of care, enabling us to develop methods tailored to individual needs. Additionally, we engage in fundamental research, including animal experiments, to generate evidence supporting new nursing techniques.

References

1. Kida R, Takemura Y, Inoue M, Ichikawa N, Koyanagi H. Nursing Management for the Temporary Lodging Facilities in Japan in the Early Stages of the COVID-19 Pandemic: A Multiple-Case Study. *Japan Journal of Nursing Science*. e12507.
2. Inoue M, Kunie K, Takemura Y. Relationship between perceived workplace reflection support and person-environment fit among hospital nurses: A cross-sectional study. *Journal of Society of Nursing Practice*. 35(1), 46-58.
3. Konya C, Ishizawa M, Takeuchi Y, Nakagami G, Kitamura A, Morita K, Abe Y, Shoji S, Shimada K, Tanaka K, Higuchi H, Mizuki T, Motegi S, Kawakami S, Sanada H. Longitudinal evaluation of pressure ulcer prevalence and estimated incidence rates using inferential statistics from the 1st to 4th nationwide surveys: Report from the 8th-term Survey Committee Working Group on Longitudinal Assessment. *Japanese Journal of Pressure Ulcers*. 2023;25(2):90-95.
4. Ishizawa M, Konya C, Kitamura A, Abe Y, Shimada K, Shoji S, Takeuchi Y, Tanaka K, Nakagami G, Higuchi H, Mizuki T, Motegi S, Nishibayashi N, Morita K. Prevalence, characteristics, locations, and severity of "pressure ulcers" combining self-inflicted pressure ulcers and medical device-related pressure injuries by place of care: Report of the 5th (FY2019-2022) Survey Committee of the Japanese Society of Pressure Ulcers. *Japanese Journal of Pressure Ulcers*. 2023;25(2):96-118.
5. Kida R, Kitamura A, Isobe T, Takemura Y. Nationwide Distribution of Facilities with Certified Nurse Administrators, and Secondary Healthcare Area and Facility Characteristics Related to their Affiliation: An Open Data Analysis using a Geographic Information System. *Journal of Japan Academy of Nursing Science*. 2023;43:305-314.
6. Inoue M, Takemura Y, Kitamura A, Isobe T. The process through which nurses providing care to COVID-19 patients recognize professional growth: A Trajectory Equifinality Model. *Japan Journal of Nursing Science*, e12577.

Department of Family Nursing

Professor

Mari Ikeda, Ph.D., R.N., P.H.N., C.C.P.

Lecturer

Sachiko Kita, Ph.D., R.M.W, R.N., P.H.N.

Assistant Professor

Mayumi Morisaki, Ph.D., R.N., P.H.N.

※The following information is the same as that of the previous year for certain reasons.

Homepage <http://www.fn.m.u-tokyo.ac.jp/>

Introduction and Organization

This department was established in 1992. Three faculty members currently serve the department: a professor, a lecturer, and an assistant professor. Enrolled at present are 1 doctoral student, and 1 administrative staff.

Education

1. Graduate Courses, School of Health Sciences and Nursing (credit hours)
 - Advanced Family Nursing I (2)
 - Advanced Family Nursing II (2)
 - Laboratory and/or Field Work on Family Nursing (16)
 - Practicum in Translational Research Nursing (2)
2. Undergraduate Courses for Students in the School of Integrated Health Sciences (credit hours)
 - Family Health (2)
 - Health Communication (1)
3. Undergraduate Courses for Nursing Students in the School of Integrated Health Sciences (credit hours)
 - Pediatric and Child Health Nursing (4)
 - Clinical Practicum in Pediatric and Child Health Nursing (2)
 - Integrated Clinical Practicum in Nursing (1)

Research

Our department research family with health problems, developmental task or encounter with changes in the community to which the family belongs. We aim to reveal the fluctuation that have occurred in the family system and create family support. Our on-going, specific research theme include the following:

1. Mental health and childcare Support during family formation;
2. Development and dissemination of nursing care focusing on attachment styles;
3. Family violence and gender-based violence
4. QOL for cancer patients and their families;
5. Development of a Pediatric Quality of Life (QOL) Inventory for children with chronic illness and their parents;
6. Lifetime support for survivors of childhood cancer and their families: treatment and care in their late effects, special needs education, and working;
7. Transitional care for children, adolescent and young adult with childhood-onset chronic diseases;
8. Research about prevention of deterioration of postpartum depression, child abuse and neglect;
9. Support for bereavement from family members.

Regarding the "Development and dissemination of nursing care focusing on attachment style," we have been disseminating the Attachment Style Interview (ASI) developed by Professor Bifulco in the UK which is translated into Japanese version as ASI-J. We also completed a translated version of the ASI-J for children between 2019 and 2021, and conducting its reliability and validity studies. Currently, we are conducting online training of the ASI-J for researchers, clinical practitioners, and graduate students.

Regarding research on family violence, we have developed a scale to measure family poly-victimization which means the co-occurrence of different types of violence, such as intimate partner violence, child abuse and elder abuse. In addition, we have developed a Training program for Child Abuse Prevention for citizens (TCAP-C) and tested the effectiveness. Since 2017, we have been conducting an international collaboration study with international scholars from eleven countries, to identify trauma recovery pathways after gender-based violence.

Studies focusing on transition such as "Transitional care for children, adolescent and young adult with childhood-onset chronic diseases" in patients with child chronic diseases has been conducted since 2016. We established a transition outpatient clinic in the University of Tokyo Hospital in June 2016 and have been providing transitional cares for patients with congenital heart disease, epilepsy, chromosomal abnormality, hematologic disease, and endocrine disease in the clinic. We also developed the tool "My Health Passport" in order for patients to summarize the information about their disease and share their experiences with others (e.g., friends and coworkers) and established evidence of its effectiveness. We collaborate with the evidence-based clinic, with regard to research, practice and graduate education.

In addition, we hold bimonthly family nursing research seminar, whereby deeper understanding of family nursing practice and research are promoted. In this we aim to enhance the quality of clinical practice and research in family nursing and contribute to the establishment of the science of family nursing.

Publications

1. Tobe H, Sakka M, Kita S, Ikeda M, Kamibepu

- K. The Efficacy of a Resilience-Enhancement Program for Mothers Based on Emotion Regulation: A Randomized Controlled Trial in Japan. *International Journal of Environmental Research and Public Health*. 2022; 19(22):14953. <http://doi.org/10.3390/ijerph192214953>
2. Sasaki N, Ikeda M, Nishi D. Long-term influence of unintended pregnancy on psychological distress: a large sample retrospective cross-sectional study. *Archives of Women's Mental Health*. 2022 Dec; 25(6): 1119-1127. DOI: 10.1007/s00737-022-01273-1
3. Kita S, Kamibappu K, Saint Arnault D. "Knitting together the lines broken apart": Recovery process to integration among Japanese survivors of intimate partner violence. *International Journal of Environmental Research and Public Health*. 2022; 30; 19(19): 12504.
4. Takemura Y, Inoue M, Ichikawa N, Kida R, Koyanagi H, Ikezaki S, Ikeda M. Key strategies for managing nursing care under the COVID-19 pandemic: A multiple-case study of nursing directors. *Journal of Nursing Management*. 2022 Nov; 30(8): 4042-4053. <http://doi.org/10.1111/jonm.13844>
5. Koutra K, Burns C, Sinko L, Kita S, Bilgin H, Saint Arnault D. Trauma recovery rubric: A mixed-method analysis of trauma recovery pathways in four countries. *International Journal of Environmental Research and Public Health*. 2022; 19(16).
6. Iwasaki T, Kou A, Harasawa N, Morishita-Kawahara M, Yamagata C, Moriya H, Ikeda M, Nagae H. Exploring the Attitudes and Needs of Advance Care Planning Practice Among the Working Generation. *Tokyo Women's Medical University Journal*. 2022; 6. <https://doi.org/10.24488/twmuj.2022004>
7. Kita S, Zeynep O, Saint Arnault D. Initial testing of components of the Cultural Determinants of Trauma Recovery (CDTR) Theory among American Gender-Based Violence survivors: Structural equation modeling. *Journal of Advanced Nursing*, 2022; 79 (4) : 1476-1492.
8. Muramoto M, Kita S, Tobe H, Ikeda M, Kamibepu K. The association between self-compassion in the postnatal period and difficult

experiences with COVID-19 pandemic-related changes during pregnancy: An observational study for women at 1 month postnatal in Japan. *Japan Journal of Nursing Science*, 2022; e12494.

9. Morisaki-Nakamura M, Suzuki S, Kobayashi A, Kita S, Sato I, Iwasaki M, Hirata Y, Sato A, Oka A, Kamibeppu K. Efficacy of a Transitional Support Program Among Adolescent Patients With Childhood-Onset Chronic Diseases: A Randomized Controlled Trial. *Frontiers in Pediatrics*. 2022.
10. Sato I, Soejima T, Ikeda M, Kobayashi K, Setoyama A, Kamibeppu K. Reliability and validity of the Japanese version of the Pediatric Quality of Life Inventory Infant Scales. *Journal of Patient-Reported Outcomes*, 2022; 6(10).
11. Hayakawa A, Sato I, Kamibeppu K, Ishida Y, Inoue M, Sato A, Shiohara M, Yabe H, Koike K, Adachi S, Atsuta Y, Yamashita T, Kanda Y, Okamoto S. Impact of chronic GVHD on QOL assessed using visual analogue scale in survivors after pediatric HSCT and those depending on QOL raters: a cross-sectional observational study in Japan. *International Journal of Hematology*. 2022; 115(1):123-128.

Department of Community Health Nursing / Public Health Nursing

Associate Professor

Kyoko Yoshioka-Maeda, Ph.D., R.N., P.H.N.

Assistant Professor

Chikako Honda, Ph.D., R.N., P.H.N.

Hiroshige Matsumoto, Ph.D., R.N., P.H.N.

Akari Maeda-Suzuki, Ph.D., R.N., P.H.N.

Homepage <https://chiikikango.m.u-tokyo.ac.jp/>

Introduction and Organization

The Department of Community Health Nursing was established in June 1992. The educational program for the public health nurse license has been established in the master's program of the graduate school since 2014. Our department is also in charge of this program.

Teaching activities

Our department aims to educate public health nurses with a research mindset and researchers with a public health nurse mindset. In the undergraduate program, we teach basic methods and theories of health promotion for individuals, families, and specific populations living in the community. The titles are as follows: Home Health Nursing, Community Health Nursing, Home Health Nursing Practice. There is a total of four credits of lecture and two credits of practicum.

In the graduate program, we teach about the advanced methods and theories in community health nursing and public health nursing. The titles are as follows: Advanced Community Health Nursing I, II, Advanced Community Health Nursing Seminar I, II and Practice

I, II.

We also offer an additional lecture/practical training as a part of the education program for public health nurse licenses. The titles are as follows: Skills for Public Health Nursing I, II, Public Health Nursing I, II, III, IV, V, VI, Public Administration for Nurses, Public Health Nursing Practice I, II.

We also supervise undergraduate/graduate students with their thesis.

Research activities

We conduct research to improve health and quality of life by understanding the nursing needs of people living in the community and those receiving care at home on an individual basis, as well as the needs of families, groups, and the community as a whole. In an aging society with a declining birth rate, it is important to support the independence of the older adults and prevent the need for nursing care. In addition, we aim to create community care systems that enable people with physical and mental disabilities to live well in their own familiar communities. It is also essential to support children throughout the community so that they can grow and develop healthily. Our research we are engaged in

contributes to the creation of a society that is conducive to a comfortable living environment, addressing the evolving needs of society and the times.

Our research is supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Ministry of Health, Labour and Welfare, and other foundations.

Ongoing research projects in our department are listed below.

1. Improving public health nursing practice and building care systems
 - Algorithms and evaluation methods for public health nursing activities using information and communication technology
 - Comprehensive community care systems
2. Development, evaluation and dissemination of programs to solve health problems at different stages of life
 - Programs to protect the health of community residents
 - Injury prevention for infants and toddlers
 - Dementia education programs in the community
3. Study on the development of professional competencies and skills of public health nurses
 - Policy making and project development by public health nurses
 - Elucidation of skills and tacit knowledge of public health nurses
4. Cutting-edge issues that do not fit into conventional frameworks
 - VR-based home visit learning materials for nursing students

5. The "Zero Missed Hip Dislocations in Infants" Project

To achieve our goal of preventing missed hip dislocation in newborns and infants, we're working together with experts in nursing, medicine, and engineering. Our goal is to develop a screening system that can be used by public health nurses and midwives

during their visits to newborns. We are also focusing on developing a comprehensive community-based approach to early treatment of this condition.

References

1. Yoshioka-Maeda, K., Matsumoto, H., Inagaki-Asano, A., & Honda, C. (2023). Community-Based Hip Screening for Up to Four-Month-Old Infants and Health Guidance for Their Caregivers in Japan: A Nation-Wide Survey. *Nursing Reports*, 13(4), 1442–1451.
2. Yoshioka-Maeda, K., Matsumoto, H., Honda, C., Shiomi, M., Taira, K., Hosoya, N., ... Miura, T. (2023). New Web-Based System for Recording Public Health Nursing Practices and Determining Best Practices: Protocol of an Exploratory Sequential Design. *JMIR Research Protocols*, 12(1), e45342.
3. Yoshioka-Maeda, K., Iwasaki-Motegi, R., & Honda, C. (2023). Resolution for the Severe Shortage of Nurses for Combating COVID-19 in Japan. *Asia Pacific Journal of Public Health*, 35(4), 320–321.
4. Amano, M., Matsumoto, H., Honda, C., & Yoshioka-Maeda, K. (2023). Predictors of parenting difficulties at the 18-month health checkups: A retrospective study using administrative data from infant health checkups. *Public Health Nursing*.
5. Matsumoto, H., Tsuda, S., Takehara, S., Yabuki, T., & Hotta, S. (2023). Association between Support after Dementia Diagnosis and Subsequent Decrease in Social Participation. *Annals of Geriatric Medicine and Research*, 27(3), 274–276.

Health Sciences and Nursing

3. Clinical Nursing

Department of Gerontological Home Care and Long-term Care Nursing/Palliative Care Nursing

Professor

Noriko Yamamoto-Mitani, Ph.D., R.N.

Associate Professor

Ayumi Igarashi, Ph.D., R.N.

Assistant Professor

Yuka Sumikawa, Ph.D., R.N.

Hanako Numata, Ph.D., R.N.

Homepage <https://longtermcare.m.u-tokyo.ac.jp/en/home-en/>

Introduction and Organization

The Department of Gerontological Home Care and Long-term Care Nursing/Palliative Care Nursing has almost 50 years of history and tradition. Originally, the department was started as the *Department of Adult Health* in 1965 and it underwent several re-organizations. The current structure with two sub-divisions of *Adult Health Nursing* and *Palliative Care Nursing* was started in 2006. Further, *Adult Health Nursing* was renamed to *Gerontological Home Care and Long-term Care Nursing* in 2016. Noriko Yamamoto-Mitani has been responsible for administration as a department chair since 2012.

Education

In the undergraduate program, our department is in charge of the lectures and clinical practicums for *adult health nursing*. In graduate education, we aim to educate students into independent researchers and competent clinicians who effectively use research. For this purpose, we respect each student's research interest that they derived from their clinical experiences. Students complete their master's thesis or

doctoral dissertation by developing a research question from their own scientific interests regarding nursing practice for older people or adults in the chronic stage.

In education, we emphasize the critical thinking process as a researcher who conducts unique and original research: from cultivating perspectives as a researcher to coming up with original research topics, developing research topics into unique research questions/ hypotheses, choosing appropriate research methods, and developing valid research protocols.

Research

In research, we aim to contribute to the development of nursing science and improvement in the quality of nursing practice through collaborative research with clinicians. Specifically, we aim to develop new nursing knowledge grounded on Japanese culture, as needed in tomorrow's aged society. Faculty members conduct studies on various topics in the field of adult and gerontological nursing.

Regarding methods, besides conventional statistical methods, we often utilize qualitative methods to understand the experiences of individual patients

and/or nurses and to conceptualize and theorize them.

1) Quality assurance and improvement for long-term care for older people

The goal of long-term care nursing is to allow older adults to live as high-quality lives as possible, even with diseases/disabilities; the paradigm of long-term care is different from that of acute care which typically aims to have the patients recover promptly from disease conditions. There has not been enough attention to long-term care nursing in today's healthcare practice; there has been little research on quality assurance and improvement in the long-term care field in Japan. In this department, we have been conducting multiple studies on long-term care in facilities and homecare nurse agencies regarding care quality assurance and improvement.

First, we attempt to develop intervention models to improve care quality in close collaboration with clinicians, including nurses and care workers. We aim to develop sustainable systems to improve their daily care practice, collaborating with nurses at long-term care facilities and homecare nurse agencies.

Second, we develop indicators to assess the quality of long-term care, including home care nursing. We have been developing them as a part of the overall assessment system needed for long-term care nursing.

Quality assurance and improvement for long-term care facilities and home-care nurse agencies grow in importance, given the educational opportunities for healthcare providers working at long-term care facilities and homecare nurse agencies are limited compared to those working at critical hospitals.

2) Establishing a case study method to develop nursing science from clinical sites

We attempt to develop a new research method that clinicians could use to conduct effective case studies. Although case study has been used for a long time, it has not had a standardized method. We aim to develop a protocol for conducting a case study that contributes to developing nursing science.

3) Establishment of support systems for older people in the integrated community care

In the Japanese aged society, establishing a local structure supporting the life of older people in the

community is an urgent need. In collaboration with different stakeholders, we strive to create programs that aim to build a dementia-friendly community (DFC). As part of this effort, we developed and evaluated a dementia awareness program for local residents that uses virtual reality (VR) technology to provide a first-person experience from the perspective of a person with dementia. As a next step, we are expanding the scope of the program from local residents to nurses working at healthcare institutions, nursing students, and children, and are modifying and evaluating the program to suit each target group.

4) Creating a workplace that supports care-work balance

In a super-aging society, the number of people caring for family members while working is increasing. Therefore, we are working on the development of e-learning programs to create a workplace that supports the balance between nursing care provision and work. Through e-learning, we are developing content that allows students to learn not only about nursing care, but also about how to respond as colleagues and superiors, and how to create a workplace. In the next fiscal year, we plan to intervene through an e-learning program developed as workplace training for companies and local governments and evaluate its effect.

5) Educational support for end-of-life care for professionals

As we enter an era of high mortality, there is a growing need for places to provide end-of-life care outside hospitals. In our department, we are working on a Multidisciplinary Educational Program for End-of-life Care in which nurses and caregivers working in homes and facilities can learn together. We have developed an e-learning program that allows them to know about end-of-life care, and we have also held group training sessions where they can learn practical methods for multi-professional collaboration. We are currently evaluating the effectiveness of these programs.

We also conduct studies on a range of topics in nursing of chronic conditions, from preventive to end-of-life phase. We have been conducting studies which are expected to allow us to understand the state

of individuals who require nursing in those periods and investigate effective and efficient nursing care for such individuals.

Publications

1. Igarashi A., Matsumoto H., Takaoka M., Kugai H., Suzuki M., Murata S., Miyahara M., Yamamoto-Mitani N. Building Relationships Between Community Care Professionals and Convenience Stores in Japan: Community-Based Participatory Research. *Prog Community Health Partnersh.* 2023;17(1):1-11. doi: 10.1353/cpr.2023.0005.
2. Takaoka M., Igarashi A., Ninomiya A., Ishibashi T., Yamamoto Mitani N. Continuous laxative use and its relationship to defecation among residents of nursing homes: A longitudinal observational study using the interRAI. *Geriatr Gerontol Int.* 2023;24(1):133-139. doi:10.1111/ggi.14777
3. Unoki T., Hayashida K., ..., Yasaka T., ..., Nishida O. Japanese Clinical Practice Guidelines for Rehabilitation in Critically Ill Patients 2023 (J ReCIP 2023). *J Intensive Care.* 2023; 11(1): 47. doi: 10.1186/s40560 023 00697-w
4. Igarashi A., Matsumoto H., Suzuki Takaoka M., Kugai H., Sakka M., Yamamoto Mitani N. Helping behaviors of community members towards older adults and the related factors: a cross-sectional study. *Psychogeriatrics.* 2023; 24(1):117-126. doi: 10.1111/psyg.13050
5. Yoshioka-Maeda K., Matsumoto H., Inagaki-Asano A., Honda C. Community Based Hip Screening for Up to Four Month Old Infants and Health Guidance for Their Caregivers in Japan: A Nation Wide Survey. *Nurs Rep.* 2023; 13(4): 1442-1451. doi: 10.3390/nursrep13040121
6. Cho E., Lee KH., Kang B., Jang J., Shin J., Eltaybani S., Yamamoto-Mitani N., Kim MJ. Perceived Work Environment, Educational Status, Staffing Levels, and Work Outcomes in Long-Term Care Settings During COVID-19. *J Am Med Dir Assoc.* 2023; 24(10):1600-1605. doi: 10.1016/j.jamda.2023.08.009.
7. Eltaybani S. Capabilities and limitations of large language models in critical care nursing research: Examples from the big three. *Nursing in Critical Care.* 2023 Nov;28(6):838-853. doi: 10.1111/nicc.12974
8. Kugai H., Igarashi A., Anezaki S., Fukui C., Saito N., Hamasaki Y., Yamamoto Mitani N. Components of peritonitis preventive self-care education programs associated with self-care knowledge and behavior among patients undergoing peritoneal dialysis in Japan: a cross-sectional study. *Ren Replace Ther.* 2023; 9(1): 34. doi: 10.1186/s41100 023 00489-w
9. Shibuta T., Waki K., Miyake K., Igarashi A., Yamamoto Mitani N., Sankoda A., Takeuchi Y., Sumitani M., Yamauchi T., Nangaku M., Ohe K. Preliminary Efficacy, Feasibility, and Perceived Usefulness of a Smartphone-Based Self-Management System with Personalized Goal Setting and Feedback to Increase Step Count Among Workers With High Blood Pressure: Before and After Study. *JMIR Cardio.* 2023; 7: e43940. doi: 10.2196/43940
10. Yoshioka-Maeda K., Matsumoto H., Honda C., Shiomi M., Taira K., Hosoya N., Sato M., Sumikawa Y., Fujii H., Miura T. New Web-Based System for Recording Public Health Nursing Practices and Determining Best Practices: Protocol of an Exploratory Sequential Design. *JMIR Res Protoc.* 2023 Jun 12;12:e45342. doi: 10.2196/45342.
11. Eltaybani S., Kawase K., Kato R., Inagaki A., Li CC., Shinohara M., Igarashi A., Sakka M., Sumikawa Y., Fukui C., Yamamoto-Mitani N. Effectiveness of home visit nursing on improving mortality, hospitalization, institutionalization, satisfaction, and quality of life among older people: Umbrella review. *Geriatr Nurs.* 2023; 51: 330-345. doi: 10.1016/j.gerinurse.2023.03.018.
12. Eltaybani S., Kitamura S., Fukui C., Igarashi A., Sakka M., Noguchi Watanabe M. Takaoka M. Inagaki A., Yasaka T. Kobayashi H., Yamamoto Mitani N. Toward developing care outcome quality indicators for home care for older people: A prospective cohort study in Japan. *Geriatr. Gerontol. Int.* 2023; 23(5): 383-394. doi: 10.1111/ggi.14578
13. Yoshioka Maeda K, Matsumoto H., Honda C., Shiomi M., Taira K., Hosoya N., Sato M., Sumikawa Y., Fujii H., Miura T. New Web Based

System for Recording Public Health Nursing Practices and Determining Best Practices: Protocol of an Exploratory Sequential Design. *JMIR Research Protocols*. 2023; 12: e45342. doi: 10.2196/45342

14. Son BK., Miura T., Yabu KI., Sumikawa Y., Kim D., Lyu W., Yang Y., Tanaka M., Tanaka T., Yoshizawa Y., Iijima K. The Co Design/Co Development and Evaluation of an Online Frailty Check Application for Older Adults: Participatory Action Research with Older Adults. *Int. J. Environ. Res. Public Health*. 2023; 20(12): 6101. doi: 10.3390/ijerph20126101

Department of Midwifery and Women's Health

Professor

Megumi Haruna, Ph.D., R.N.M.

Lecturer

Kaori Yonezawa, Ph.D., R.N.M.

Assistant Professor

Yuriko Usui, Ph.D., R.N.M.

Assistant Professor

Yuko Kato, R.N.M.

Homepage <http://midwifery.m.u-tokyo.ac.jp/>

Introduction and Organization

The Department of Midwifery and Women's Health was established in 2002.

It has 4 faculty members introduced above, 1 JSPS postdoctoral fellowship for overseas researcher, 1 postdoctoral research fellow, 15 graduate students (5 in master's courses, 9 in doctoral courses), and 11 visiting researchers.

Teaching activities

We have graduate and undergraduate courses.

1. Graduate Courses, School of Health Sciences and Nursing
 - 1) Advanced Midwifery and Women's Health I (2 credits, lectures)
 - 2) Advanced Midwifery and Women's Health II (2 credits, lectures)
2. Graduate Courses, School of Health Sciences and Nursing for midwifery
 - 1) Midwifery I (2 credits, lectures)
 - 2) Midwifery II (2 credits, lectures)
 - 3) Midwifery III (2 credits, lectures)

- 4) Midwifery IV (2 credits, lectures)
- 5) Midwifery V (2 credits, lectures)
- 6) Midwifery VI (1 credit, lectures)
- 7) Clinical Practicum of Administration for Midwifery (1 credit, practices)
- 8) Clinical Practicum in Midwifery I (2 credits, practices)
- 9) Clinical Practicum in Midwifery II (8 credits, practices)

3. Undergraduate Courses of Nursing, School of Health Sciences and Nursing
 - 1) Maternal-Newborn Nursing (2 credits, lectures)
 - 2) First AID course (1 credit, lecture)
 - 3) Clinical Practicum in Maternal-Newborn Nursing (2 credits, practices)

Research activities

Our research activities encompass the field of maternal and child health emphasizing on the promotion of women's health and quality of life at every stage of life.

We aim to conduct the following research projects:

1. Creating evidence of health guidance during pregnancy

- 1) Healthy lifestyle: Adequate maternal nutrition, weight management, exercise, physical activity, sleep, and mental health are needed to ensure a healthy lifestyle among pregnant women.
We aim to conduct the Japan Pregnancy, Eating, Activity, Cohort Study (J-PEACH study) to provide evidence for appropriate health guidance. It investigates maternal body weight, glucose and lipid metabolite biomarkers, nutritional intakes, and physical activities to optimize weight management and a healthy lifestyle during pregnancy to prevent adverse perinatal outcomes including low birth weight.
2. Development of a support system for reliable childbirth
 - 1) Midwifery care for positive childbirth experiences
This study evaluates the care provided by midwife-led system and in-hospital midwifery clinic with the aim of building a positive and efficient midwifery care for a positive birth experience for the mother.
 - 2) “Fear of childbirth” and psychosocial factors among pregnant Japanese women
This study aims to identify the psychosocial risk factors of intense fear of childbirth.
 - 3) Development of assessment methods of birth canal using transperineal ultrasonography
This study aims to develop the objective assessment methods of birth canal and the association of birth canal and delivery mode using transperineal ultrasonography.
 - 4) Evaluation of learning efficacy of Virtual Reality on midwifery education
Collaborative research between the University of the Sunshine Coast, Queensland, Australia and the Waikato Institute of Technology, New Zealand is conducted to create and evaluate educational content related to midwifery using virtual reality technology. Furthermore, a 360° camera is being used to create teaching materials and to study its effectiveness in midwifery education.
 - 5) Development and effectiveness of an online Japanese version of mindfulness-based childbirth and parenting program
This study aims to develop a short online Japanese version of the Mindfulness-Based Childbirth and Parenting (MBCP) program and to investigate the program’s effectiveness on women’s prenatal mental health.
3. Development of a support system for postpartum body management
 - 1) Pelvic floor disorders among postpartum women
This study evaluates the effect of pelvic floor muscle training in prevention of postpartum pelvic floor disorders (e.g., urinary incontinence). Furthermore, this study aims to develop and implement a pelvic floor muscle training program.
4. Development of a support system for women’s health
 - 1) Health Support for working mothers and women
This study investigates the cadences of daily life and conditions of sleep such as excessive daytime sleepiness and other related factors among working mothers. Furthermore, it also explores factors associated with work engagement among working pregnant women.
 - 2) Support for breastfeeding mothers and babies
This study aims to develop the Japanese version of the Infant Breastfeeding Assessment Tool (IBFAT), to assess the instinctive feeding behavioral reflexes of newborns, and explore factors affecting the IBFAT.
5. Creating evidence of health guidance for neonatal skin care
 - 1) Development of an effective skin care intervention to prevent neonatal skin problems.
This study investigates the effect of following a moisturizing skincare routine on improving skin barrier functions among healthy neonates. Moreover, we will investigate the relationship between newborns’ skin problems and allergies (i.e., food allergy or atopic dermatitis).
 - 2) Effect of skincare on skin barrier function and normal bacterial flora
This study investigates the effect of skin care, including bathing, on infants’ skin. It focuses on skin barrier function and normal bacterial flora

as a skin condition.

Publications

1. Yonezawa, K., Kido, M., Haruna, M., Sasagawa, E., Usui Y. A cross-national survey of patterns of complementary foods for infants. *J. Jpn. Acad. Midwif.* 2023 Nov 24;37(3): 265-272. doi: 10.3418/jjam.JJAM-2023-0022
2. Yonezawa K, Haruna M. Relationship Between Degree of Neonatal Physiologic Desquamation and Skin Barrier Function. *J Perinat Neonatal Nurs.* 2023 Oct-Dec 01;37(4):348-353. doi: 10.1097/JPN.0000000000000694. Epub 2023 Apr 27. PMID: 37115943.
3. Usui Y, Takegata M, Takeda S, Kitamura T. Relationships between Depression, Fear of Childbirth, and Obsessive-Compulsive Symptoms among Pregnant Women under the COVID-19 Pandemic in Japan. *Healthcare (Basel).* 2023 Jan 27;11(3):361. doi: 10.3390/healthcare11030361. PMID: 36766936; PMCID: PMC9914326.
4. Pathirathna ML, Nandasena HMRKG, Samarasekara BPP, Dasanayake TS, Weerasekara I, Haruna M. Is Maternal Carbohydrate Intake Having an Impact on Newborn Birth Weight? A Systematic Review. *Nutrients.* 2023 Mar 28; 15(7):1649. doi: 10.3390/nu15071649. PMID: 37049491; PMCID: PMC10096855.
5. Tomita A, Tahara-Sasagawa E, Yonezawa K, Usui Y, Haruna M. Reliability and validity of the Japanese version of the Infant Breastfeeding Assessment Tool. *Midwifery.* 2023 Jun;121: 103670. doi: 10.1016/j.midw.2023.103670. Epub 2023 Mar 26. PMID: 37019001.
6. Nishihara N, Haruna M, Usui Y, Yonezawa K, Hikita N, Sasagawa E, Nakano K, Tanaka M, Ohori R, Aoyama S, Sasaki S, Fujita M, Matsuzaki M, Suetsugu Y, Sato Y. Dietary Intake and Its Association with Birth Outcomes in Women with Nausea and Vomiting during the Second Trimester of Pregnancy: A Prospective Cohort Study in Japan. *Nutrients.* 2023 Jul 29; 15(15):3383. doi: 10.3390/nu15153383. PMID: 37571320; PMCID: PMC10421251.
7. Shimizu S, Yonezawa K, Haruna M, Tahara-Sasagawa E, Usui Y, Minematsu T, Higuchi S. Relationship between facial skin problems with a focus on inflammatory cytokines and the presence of *Malassezia* in 1-month-old infants. *Sci Rep.* 2023 Mar 28;13(1):5041. doi: 10.1038/s41598-023-31949-2. PMID: 36977695; PMCID: PMC10049982.
8. Kanai R, Tahara-Sasagawa E, Yonezawa K, Hikita N, Usui Y, Maejima M, Haruna M. Association of work engagement with job resources and perceived symptoms among working pregnant women: A cross-sectional study. *J. Jpn. Acad. Midwif.* 2023 Aug 25;37(3): 231-242. doi: 10.3418/jjam.JJAM-2023-0004
9. Maejima M, Yonezawa K, Sasagawa E, Hikita N, Usui Y, Haruna M. Psychological factors of pregnant women associated with inadequate maternal weight gain in Japan. *J Matern Fetal Neonatal Med.* 2023 Dec;36(1):2217466. doi: 10.1080/14767058.2023.2217466. PMID: 37263626.
10. Wakabayashi N, Haruna M, Yonezawa K, Sasagawa E, Usui Y, Ohori R, Aoyama S, Sasaki S, Nagamatsu T; Tokyo area members of the J-PEACH Study group as of 2019–2022. Association of serum docosahexaenoic acid and eicosapentaenoic acid levels with dietary intakes and supplement use during pregnancy: a prospective observational study. *J Nutr Sci.* 2023 Dec 14;12:e125. doi: 10.1017/jns.2023.105. PMID: 38155803; PMCID: PMC10753464.
11. Yamauchi R, Haruna M, Yonezawa K, Usui Y, Tahara-Sasagawa E, Maeda Y, Ikeda Y. Factors associated with ambition for promotion among female and male workers: a cross-sectional study in Japan. *CSRDA Discussion Paper Series*, 2023; No.68. <https://csrdadps.com/paper/68>
12. Tahara-Sasagawa E, Mochida K, Sadamori T, Suzuki M, Guerrero C, Haruna M, Misago C. Lessons from the "Humanization of Childbirth" Projects: Qualitative analysis of seven projects funded by the Japan International Cooperation Agency. *Glob Health Med.* 2023 Oct 31;5(5): 301-305. doi: 10.35772/ghm.2023.01054. PMID: 37908509; PMCID: PMC10615027.
13. Hikita N, Batsaikhan E, Sasaki S, Haruna M, Yura A, Oidovsuren O. Evaluation of salt intake estimated from 24-h urinary sodium excretion in medical professionals in Darkhan-Uul Province,

- Mongolia: a cross-sectional study. *Sci Rep.* 2023 Jun 28;13(1):10456. doi: 10.1038/s41598-023-37631-x. PMID: 37380730; PMCID: PMC10307767.
14. Murayama R, Ashida S, Minatani M, Matsuzaki M, Yoshida M, Haruna M. Symptoms of pelvic organ prolapse and related factors during five years after vaginal delivery: A cross-sectional study. *J. Jpn. Acad. Midwif.* 2023 Aug 17;37(3):243-251. doi: 10.3418/jjam.JJAM-2023-0012
 15. Takegata M, Usui Y, Sohda S, Takeda S, Takeda J, Saito T, Kasai Y, Watanabe H, Haruna M, Ohashi Y, Kitamura T. Tokophobia: Case Reports and Narratives of Ten Japanese Women. *Healthcare (Basel).* 2023 Feb 26;11(5):696. doi: 10.3390/healthcare11050696. PMID: 36900701; PMCID: PMC10001124.
 16. Son BK, Miura T, Yabu KI, Sumikawa Y, Kim D, Lyu W, Yang Y, Tanaka M, Tanaka T, Yoshizawa Y, Iijima K. The Co-Design/Co-Development and Evaluation of an Online Frailty Check Application for Older Adults: Participatory Action Research with Older Adults. *Int J Environ Res Public Health.* 2023 Jun 10;20(12):6101. doi: 10.3390/ijerph20126101. PMID: 37372688; PMCID: PMC10297892.
 17. Yoshimura M, Fujita M, Shibata A, Ohori R, Aoyama S, Yonezawa K, Sato Y, Sasaki S, Matsuzaki M, Suetsugu Y, Haruna M. Association of Eicosapentaenoic and Docosa-hexaenoic Acid Intake with Low Birth Weight in the Second Trimester: The Japan Pregnancy Eating and Activity Cohort Study. *Nutrients.* 2023 Nov 18;15(22):4831. doi: 10.3390/nu15224831. PMID: 38004224; PMCID: PMC10674964.
 18. Shibata A, Fujita M, Yamaguchi S, Yoshimura M, Murakami-Sekimata A, Sekimata M, & Haruna M. Association of Salivary Porphyromonas gingivalis with Frequency of Meals, Smoking history and Oral care in Pregnant women: A cross-sectional study. *JNSE.* 2023;10: 211-220. doi: 10.24462/jnse.10.0_211
 19. Kitamura T, Usui Y, Wakamatsu M, Minatani M, Hada A. What Are The Core Symptoms of Antenatal Depression? A Study Using Patient Health Questionnaire-9 among Japanese Pregnant Women in the First Trimester. *Healthcare (Basel).* 2023 May 20;11(10):1494. doi: 10.3390/healthcare11101494. PMID: 37239780; PMCID: PMC10218321.
 20. Ohashi Y, Takegata M, Takeda S, Hada A, Usui Y, Kitamura T. Is Your Pregnancy Unwanted or Unhappy? Psychological Correlates of a Cluster of Pregnant Women Who Need Professional Care. *Healthcare (Basel).* 2023 Aug 3;11(15):2196. doi: 10.3390/healthcare11152196. PMID: 37570436; PMCID: PMC10418804.
 21. Hada A, Ohashi Y, Usui Y, Kitamura T. A Scale of Parent-to-Child Emotions (SPCE): Development and validation of a short form. *PCN Rep.* 2023 Oct 4;2(4):e148. doi: 10.1002/pcn5.148. PMID: 38868730; PMCID: PMC11114296.
 22. Kishino S, Tahara-Sasagawa E, Yonezawa K, Usui Y, Misago C, Haruna M. The relationship between “Intrapartum care for a positive childbirth experience” and satisfaction with care in obstetrics: Analysis of data at the National Women's Hospital in El Salvador. *J. Jpn. Acad. Midwif.* 2023 Mar;37(1):72-84. doi: 10.3418/jjam.JJAM-2022-0011 (in Japanese)

Department of Psychiatric Nursing

Professor

Daisuke Nishi, M.D., Ph.D.

Associate Professor

Yuki Miyamoto, R.N., P.H.N., M.H.S.W., Ph.D.

Homepage [http:// plaza.umin.ac.jp/heart/](http://plaza.umin.ac.jp/heart/)

Introduction and Organization

Our department was firstly established as Department of Fourth Clinical Medical Nursing in School of Health Care and Nursing in 1957. When the School of Health Care and Nursing was reorganized as the School of Health Sciences in 1965, the department was renamed Department of Mental Health. In 1992, as School of Health Sciences became The School of Health Science and Nursing, Department of Mental Health became Department of Mental Health and Psychiatric Nursing. As the result of the shift to the chair system of the Graduate School of Medicine in 1996, two departments were established, Department of Mental Health and Department of Psychiatric Nursing. Faculty, staff, and students of two departments have been working cooperatively ever since.

Our department currently has two faculty members introduced above, part-time lecturers, visiting research fellows, doctoral course students, master course students, and research associates.

Our department's mission comprises two elements. One is to provide education and research training in mental health and psychiatric nursing to undergraduate and graduate students in order to prepare students to assume leadership roles in nursing clinical practice, administration, teaching, and research in this field. The other is to conduct clinical research in the fields of psychiatric nursing and advance knowledge and theory through research.

All activities of our department are conducted in collaboration with staff members in the Department of Mental Health.

Education

Our department is responsible for giving lectures on psychiatric nursing to undergraduate students. Other than lectures, our department provides students opportunities to practice psychiatric nursing activities in several relevant facilities.

Our department is also obliged to educate graduate students in master and doctor programs in psychiatric nursing. To accomplish this objective, our department has a specialized lecture course on psychiatric nursing, and seminars on mental health and psychiatric nursing for graduate students. These activities are conducted and supervised by the faculty. In collaboration with the department of mental health, we also have the department seminar every Wednesday evening, where members provide the actual plans for their own research and discuss the topic.

We also have a variety of study clubs. We have psychiatric nursing study club, study group for multi-level analysis, qualitative research study group, and so on.

Research

Our research field covers mental health and psychiatric nursing. Our department has many research projects across diverse fields as follows: study of self-management in mental health; recovery in people with mental health difficulties; community support system for the people with mental health needs; peer support; stigma; social inclusion; mental health in people with substance use disorder or

physical diseases; mental health in nurses or other workers; disaster mental health nursing; trauma-informed care, and reducing the use of seclusion and restraint. We are conducting studies in collaboration with researchers in other institutions and universities.

One of our research topics is "recovery," a concept that has proximity and overlap with quality of life among people who have experienced mental health difficulties. Recovery is a dynamic concept that includes restoring life, which means developing the individuals' aspirations for their life and getting back the life they want to live. In Japan, mental health care is changing and will increasingly need to emphasize the quality of life and recovery of those who have experienced mental health difficulties.

Some examples of our research work on recovery include (1) Accumulating the narratives of people who have experienced mental illness. (2) Developing patient-reported outcome measures that people with mental disorders feel are relevant to their lives. (3) Developing practices that enhance the well-being of people with and without mental disorders. We are also involved in a range of other projects.

It is necessary to pursue research involving people who have experience of mental health difficulties. We are co-producing research with people who have experienced mental health difficulties (patient and public involvement in designing and conducting research). There is a need to share the premise that any person's thoughts and opinions are important and valuable. We aim to improve mental health and medical welfare and to contribute to the realization of a society in which individuals feel that they are respected as they are.

Publications

1. Nakanishi M, Nakashima T, Miyamoto Y, Sakai M, Yoshii H, Yamasaki S, Nishida A. Association between advance care planning and depressive symptoms among community-dwelling people with dementia: An observational cross-sectional study during the COVID-19 pandemic in Japan. *Front Public Health*. 2023 Mar 30;11:915387. doi:10.3389/fpubh.2023.915387.
2. Iida M, Sakuraya A, Imamura K, Asaoka H, Arima H, Ando E, Inoue A, Inoue R, Iwanaga M, Eguchi H, Otsuka Y, Kobayashi Y, Komase Y, Kuribayashi K, Sasaki N, Tsuno K, Hino A, Watanabe K, Ebara T, Shimazu A, Kawakami N, Tsutsumi A. Effects of participatory organizational interventions on mental health and work performance: A protocol for systematic review and meta-analysis. *Journal of Occupational Health*. 2023:uia028.
3. Funakoshi A, Miyamoto Y, Tsuchiya T, Tsunoda A. A. Development of the clinical competency assessment scale in child and adolescent mental health nursing. *Journal of Psychiatric and Mental Health Nursing*. 2023;00:1-13. doi:10.1111/jpm.13014.
4. Hayes D, Hunter-Brown H, Camacho E, McPhilbin M, Elliott RA, Ronaldson A, Bakolis I, Repper J, Meddings S, Stergiopoulos V, Brophy L, Miyamoto Y, Castelein S, Klevan TG, Elton D, Grant-Rowles J, Kotera Y, Henderson C, Slade M, De Ruyscher C, Okoliyski M, Kubinová P, Eplov LF, Toernes C, Narusson D, Tinland A, Puschner B, Hiltensperger R, Lucchi F, Borg M, Tan RBM, Sornchai C, Tiengtom K, Farkas M, Morland-Jones H, Butler A, Mpango R, Tse S, Kondor Z, Ryan M, Zuaboni G, Hanlon C, Harcla C, Vanderplasschen W, Arbour S, Silverstone D, Bejerholm U, Powell CL, Ochoa S, Garcia-Franco M, Tolonen J, Dunnett D, Yeo C, Stepanian K, Jebara T. Organisational and student characteristics, fidelity, funding models, and unit costs of recovery colleges in 28 countries: a cross-sectional survey. *The Lancet Psychiatry*. 2023;10(10):768-79.
5. Kawaguchi T, Abe M, Yamaguchi S, Igarashi M, Ogawa M, Shiozawa T, Yasuma N, Sato S, Miyamoto Y, Fujii C. Opinion on the research phase and themes of patient and public involvement in the research of community mental health and welfare: A qualitative content analysis based on multiple stakeholders' perspectives. [in Japanese] *Iryo to Shakai*. 2023; 33(2):257-270. <https://doi.org/10.4091/iken.2023.001>
6. Igarashi M, Miyamoto Y, Watanabe K. The barriers and support experienced by university students who use mental health services. [in Japanese] *Japanese Journal of College Mental Health*. 2023; 5:92-100.

7. Iiyama S, Izutsu T, Miyamoto Y, Benavidez JRM, Tsutsumi A. Effectiveness of Psychological First Aid e-Orientation among the General Population in Muntinlupa, the Philippines. *International Journal of Environmental Research and Public Health*. 2023; 20(2): 983. doi:10.3390/ijerph 20020983
8. Dohi Y, Imamura K, Sasaki N, Komase Y, Sakuraya A, Nakamura Y, Maejima M, Aoyama M, Kawakami N, Miyamoto Y. (2023). Effects of an internet-delivered behavioral activation program on improving work engagement among Japanese workers: A pre-and post-test study. *J Occup Environ Med*. 65 (10)
9. Sasaki N, Tabuchi T, Okubo R, Nishi D. Association of living condition using urbanisation level and neighbourhood deprivation with loneliness and social isolation during COVID-19 pandemic: a cross-sectional study of the nationwide data in Japan. *BMJ Public Health*. 2023;1(1):e000341.
10. Obikane E, Watanabe K, Nishi D, Kawakami N. Adverse childhood experiences and personal values in adolescence: A cross-sectional study using community adult samples in Japan. *Pediatr Int*. 2023 Jan;65(1):e15370. doi:10.1111/ped. 15370. PMID: 36165851.
11. Kataoka M, Hazumi M, Usuda K, Okazaki E, Nishi D. Association of preexisting psychiatric disorders with post-COVID-19 prevalence: a cross-sectional study. *Sci Rep*. 2023 Jan 7;13(1): 346. doi: 10.1038/s41598-023-27405-w. PMID: 36611076; PMCID: PMC9823253.
12. Obikane E, Nishi D, Ozaki A, Shinozaki T, Kawakami N, Tabuchi T. Association between Poverty and Refraining from Seeking Medical Care during the COVID-19 Pandemic in Japan: A Prospective Cohort Study. *Int J Environ Res Public Health*. 2023 Feb 2; 20(3): 2682. doi: 10.3390/ijerph20032682. PMID: 36768046; PMCID: PMC9915459.
13. Iwanaga M, Nishi D, Obikane E, Kawakami N. Age of victimization and moderating role of social support for the relationship between school-age bullying and life satisfaction in middle-age. *Scand J Public Health*. 2023 Feb 2: 14034948221148788. doi: 10.1177/1403494822 1148788. Epub ahead of print. PMID: 36732917.
14. Kazdin AE, Wu CS, Hwang I, Puac-Polanco V, Sampson NA, Al-Hamzawi A, Alonso J, Andrade LH, Benjet C, Caldas-de-Almeida JM, de Girolamo G, de Jonge P, Florescu S, Gureje O, Haro JM, Harris MG, Karam EG, Karam G, Kovess-Masfety V, Lee S, McGrath JJ, Navarro-Mateu F, Nishi D, Oladeji BD, Posada-Villa J, Stein DJ, Üstün TB, Vigo DV, Zarkov Z, Zaslavsky AM, Kessler RC; WHO World Mental Health Survey collaborators. Antidepressant use in low- middle- and high-income countries: a World Mental Health Surveys report. *Psychol Med*. 2023 Mar;53(4):1583-1591. doi: 10.1017/ S0033291721003160. Epub 2021 Sep 23. PMID: 37010212; PMCID: PMC10071359.
15. Kataoka M, Kotake R, Asaoka H, Miyamoto Y, Nishi D. Research note reliability and validity of Japanese version of the trauma-informed care provider survey (TIC provider survey). *BMC Res Notes*. 2023 May 2;16(1):68. doi: 10.1186/ s13104-023-06337-8. PMID: 37131236; PMCID: PMC10152421.
16. Fukasawa M, Nishi D, Umeda M, Akiyama T, Horikoshi N, Yasumura S, Yabe H, Suzuki Y, Bromet EJ, Kawakami N. Effects of disaster-related traumatic events on worry about radiation and COVID-19: A decade after the Fukushima nuclear power plant accident. *J Psychiatr Res*. 2023 Jul; 163:135-141. doi: 10.1016/j.jpsychires. 2023.05.054. Epub 2023 May 16. PMID: 37210831.
17. Arakawa Y, Haseda M, Inoue K, Nishioka D, Kino S, Nishi D, Hashimoto H, Kondo N. Effectiveness of mHealth consultation services for preventing postpartum depressive symptoms: a randomized clinical trial. *BMC Med*. 2023 Jun 26; 21(1):221. doi: 10.1186/s12916-023-02918-3. PMID: 37365535; PMCID: PMC10294407.
18. Sasaki N, Tabuchi T, Fujiwara T, Nishi D. Adverse childhood experiences and living in the socially deprived areas in adulthood: a cross-sectional study of the nationwide data in Japan. *BMC Public Health*. 2023 Aug 24;23(1):1616. doi: 10.1186/s12889-023-16557-z. PMID: 37620789; PMCID: PMC10463887.

19. Hazumi M, Kataoka M, Usuda K, Narita Z, Okazaki E, Nishi D. Difference in the risk of discrimination on psychological distress experienced by early wave infected and late wave infected COVID-19 survivors in Japan. *Sci Rep*. 2023 Aug 12;13(1):13139. doi: 10.1038/s41598-023-40345-9. PMID: 37573383; PMCID:PMC10423270.
20. Nakayama R, Nishi D, Sato M, Ito A, Uchiyama K, Higuchi Y, Takahashi H, Ohinata K. The Effect of the Rice Endosperm Protein Hydrolysate on the Subjective Negative Mood Status in Healthy Humans: A Randomized, Double-Blind, and Placebo-Controlled Clinical Trial. *Nutrients*. 2023 Aug 7; 15(15): 3491. doi: 10.3390/nu15153491. PMID: 37571427; PMCID: PMC10421398.
21. Asaoka H, Koido Y, Kawashima Y, Ikeda M, Miyamoto Y, Nishi D. Association Between Attitudes Toward Trauma Informed Care and Psychological First-Aid Training Experience Among Health Care Professionals in Japan. *Disaster Med Public Health Prep*. 2023 Aug 3; 17:e443. doi: 10.1017/dmp.2023.103. PMID: 37533366.
22. McGrath JJ, Al-Hamzawi A, Alonso J, Altwaijri Y, Andrade LH, Bromet EJ, Bruffaerts R, de Almeida JMC, Chardoul S, Chiu WT, Degenhardt L, Demler OV, Ferry F, Gureje O, Haro JM, Karam EG, Karam G, Khaled SM, Kovess-Masfety V, Magno M, Medina-Mora ME, Moskalewicz J, Navarro-Mateu F, Nishi D, Plana-Ripoll O, Posada-Villa J, Rapsey C, Sampson NA, Stagnaro JC, Stein DJ, Ten Have M, Torres Y, Vladescu C, Woodruff PW, Zarkov Z, Kessler RC; WHO World Mental Health Survey Collaborators. Age of onset and cumulative risk of mental disorders: a cross-national analysis of population surveys from 29 countries. *Lancet Psychiatry*. 2023 Sep; 10(9): 668-681. doi: 10.1016/S2215-0366(23)00193-1. Epub 2023 Jul 30. PMID: 37531964; PMCID: PMC10529120.
23. Sasaki N, Nishi D. Euthymia scale as a protective factor for depressive symptoms: a one-year follow-up longitudinal study. *BMC Res Notes*. 2023 Sep 22;16(1):230. doi: 10.1186/s13104-023-06512-x. PMID: 37740233; PMCID:PMC10517524.
24. Honyashiki M, Decoster J, Lo WTL, Shimazu T, Usuda K, Nishi D. Mental Health Reform Processes and Service Delivery Shift From the Hospital to the Community in Belgium and Hong Kong. *Health Serv Insights*. 2023 Nov 9; 16: 11786329231211777. doi: 10.1177/11786329231211777. PMID: 37953915; PMCID: PMC10637138.
25. Kanamori Y, Miyamoto Y, Sawada U, Iida M, Tabuchi T, Nishi D. Association between adverse childhood experience and unintended pregnancy among Japanese women: a large-scale cross-sectional study. *J Psychosom Obstet Gynaecol*. 2023 Dec;44(1):2274295. doi: 10.1080/0167482X.2023.2274295. Epub 2023 Oct 26. PMID: 37882689.
26. Obikane E, Nishi D, Morisaki N, Tabuchi T. Risk factors of paternal perinatal depression during the COVID-19 pandemic in Japan. *J Psychosom Obstet Gynaecol*. 2023 Dec;44(1):2245556. doi: 10.1080/0167482X.2023.2245556. PMID: 37615367.
27. Asaoka H, Sasaki N, Koido Y, Kawashima Y, Ikeda M, Miyamoto Y, Nishi D. Reliability and validity of the Japanese version of the Professional Fulfillment Index among healthcare professionals: A validation study. *J Occup Health*. 2023 Jan-Dec;65(1): e12422. doi: 10.1002/1348-9585.12422. PMID: 37771204; PMCID: PMC10539683.
28. Sasaki N, Kuroda R, Mikami Y, Tsuno K, Imamura K, Nishi D, Kawakami N. Working environment at home and mental health in employees working from home in Japan during COVID-19 pandemic: A cross-sectional study. *J Occup Health*. 2023 Jan-Dec; 65(1): e12410. doi: 10.1002/1348-9585.12410. PMID: 37337405; PMCID: PMC10279940.
29. Iwanaga M, Iida M, Sasaki N, Kotake R, Morita Y, Asaoka H, Nozawa K, Iwanaga H, Kawakami N. Association between school bullying experience and work-related subjective well-being: A systematic review. *Environmental and Occupational Health Practice*. 2023. doi: 10.1539/eohp.2022-0026-RA

30. Sasaki N, Imamura K, Nishi D, Watanabe K, Asaoka H, Sekiya Y, Tsuno K, Kobayashi Y, Obikane E, Kawakami N. The effect of internet-based acceptance and commitment therapy (iACT) on psychological well-being among working women with a pre-school child: A randomized controlled trial. *Journal of Contextual Behavioral Science*. 2023;28:33-47.
31. Kawakami N, Sasaki N, Asaoka H, Kuroda R, Tsuno K, Imamura K. Effects of workplace measures against COVID-19 and employees' worry about them on the onset of major depressive episodes: A 13-month prospective study of full-time employees. *Journal of affective disorders*. 2023;322:187-93.
32. Watanabe K, Imamura K, Eguchi H, Hidaka Y, Komase Y, Sakuraya A, Inoue A, Kobayashi Y, Sasaki N, Tsuno K, Ando E, Arima H, Asaoka H, Hino A, Iida M, Iwanaga M, Inoue R, Otsuka Y, Shimazu A, Kawakami N, Tsutsumi A. Usage of the Brief Job Stress Questionnaire: A Systematic Review of a Comprehensive Job Stress Questionnaire in Japan from 2003 to 2021. *International Journal of Environmental Research and Public Health*. 2023; 20(3):1814.
33. Sakuraya A, Iida M, Imamura K, Ando E, Arima H, Asaoka H, Eguchi H, Hidaka Y, Hino A, Inoue A, Inoue R, Iwanaga M, Kobayashi Y, Komase Y, Otsuka Y, Sasaki N, Shimazu A, Tsuno K, Watanabe K, Kawakami N, Tsutsumi A. A proposed definition of participatory organizational interventions. *Journal of occupational health*. 2023;65(1):e12386.

Department of Gerontological Nursing / Wound Care Management

Professor

Gojiro Nakagami, Ph.D., R.N.

Assistant Professor

Mari Abe, Ph.D., R.N., Toshiaki Takahashi, Ph.D., R.N., Yuko Mugita, Ph.D., R.N.

※The following information is the same as that of the previous year for certain reasons.

Homepage <http://www.rounenkango.m.u-tokyo.ac.jp/index-e.html>

Introduction and Organization

The Department of Gerontological Nursing was established in June 2003, followed by the establishment of the Department of Wound Care Management in April 2006. We have been promoting the education of undergraduate and graduate students, clinical activities in hospitals relating to pressure injuries and diabetic foot, and research activities on the topics of gerontological nursing, wound care management, and nursing science and engineering.

Our department has established several departments: Department of Life Support Technology (Molten), Department of Advanced Skin Care (Miss Paris), Department of Advanced Nursing Technology, Department of Skincare Science, and Department of Imaging Nursing Science. We have been promoting collaborative research among government, industry and academia, as well as integrating multiple disciplines across campus.

In April 2017, the Global Nursing Research Center (GNRC) was established with the aim to create a transdisciplinary research and educational environment that fosters young researchers in nursing science in order to promote care innovation. Professor Sanada, former head of the department, served as the first director of the center until March 2022, and faculty

staff members in our department have been involved in the Division of Care Innovation in GNRC as a concurrent position.

The former head of the department, Professor Hiromi Sanada (currently Professor Emerita of the University of Tokyo) retired in March 2022, and Professor Gojiro Nakagami took over as the new head of this department in April 2022. Gerontological Nursing and Wound Care Management is currently headed by one professor and assisted by three assistant professors, a project academic specialist, an assistant clerk, seven part-time lecturers for undergraduate courses, and seven part-time lecturers for graduate courses. The student body consists of five doctoral course students and five master's course students. Our mission statement is "We wish to create a society that respects the beauty of aging and recognizes it as to be a joyful process in life."

Teaching activities

1. Undergraduate course

For undergraduate education, our department takes part in lectures of Health Support Practice, Overview of Clinical Medicine, and Observation of Human Anatomy, as well as lectures, exercises, and clinical practice about gerontological nursing and nursing

science and engineering.

1) Health Support Practicum (W in 2nd yr; 1 credit)

Nursing is a science of searching for ways to support health and the achievement of self-actualization, and it is practiced in various social situations, including hospitals, healthcare centers or medical facilities. The aim of this practicum is for students to understand the variety and wide potential of nursing, and to learn the methods and practices for health support through experiential learning of various types of nursing from the earliest stages of their nursing course. In 2022, we conducted an onsite and online practicum and the program included themes related to:

- a) Policy creation for solving problems confronted in nursing
- b) Health support service
- c) Nursing-based hospital management
- d) Development of medical devices for supporting patients' lives.

2) Overview of Clinical Medicine (S1 in 3rd yr; 2 credits)

The aim of this series of lectures is to learn the basic knowledge and thought processes for understanding clinical medicine, and to learn the pharmaceuticals required for nursing practice. The main content themes in the 2022 session included:

- a) Introduction to surgical treatment
- b) Introduction to radiology
- c) Surgical anesthesia
- d) Perioperative management
- e) Clinical conditions
- f) Natural history and treatment of diseases
- g) Nursing pharmaceuticals

The above lectures were provided through cooperation from the departments at The University of Tokyo Hospital.

3) Observation of Human Anatomy (A1 in 3rd yr; 1 credit)

The aim of this series of lectures is to gain a deeper understanding of life and learn about human anatomy through a careful examination of “death” and “disease,” as conceptual opposites of “life” and “health.” The main themes in the 2022 curriculum included:

- a) Introduction to anatomical pathology
- b) Case studies
- c) Introduction to anatomicopathological research
- d) Anatomy using ultrasound equipment
- e) Visit to specimen room

4) Gerontological Nursing (A2 in 3rd yr; 2 credits)

A series of lectures with the aim of understanding the physical, psychological, and social characteristics of the elderly population; to learn fundamental theories of gerontological nursing; and to promote an understanding of the ailments and conditions required to provide proper care to the elderly. The main themes covered in the 2022 session were as follows:

- a) Practical simulation for gerontological nursing
- b) Physical, psychological, and social characteristics of the elderly from a nursing standpoint
- c) Geriatric syndrome and nursing (i.e., dementia, walking disability, pressure injury, incontinence)
- d) Age-related changes in the physiological system
- e) Aging and dementia
- f) Aging and osteoporosis
- g) Aging and renal function, hypertension, and stroke
- h) Aging and cardiovascular disorders
- i) Aging and respiratory disorders
- j) Pharmacological management of the elderly
- k) Use of ultrasonography in nursing
- l) Nutritional management for the elderly
- m) Relationship-building and communication skills with the elderly

A portion of the above lectures was provided through cooperation from the Department of Geriatric Medicine and other departments at The University of Tokyo Hospital.

5) Clinical Practicum in Gerontological Nursing (A1 in 4th yr; 2 credits)

The aim of this practicum is to gain the holistic understanding of the elderly, learn the perspective and role functions of nursing for the elderly, and be able to think about the issues and future of gerontological nursing. In 2022, the practice was conducted online and consisted mainly of online interviews and activities with senior volunteers, case scenario exercises, lectures on multidisciplinary cooperation in each geriatric care setting (hospital, geriatric health care facility, and home), remote observation of actual

geriatric nursing care, practice ultrasound techniques that can be utilized in geriatric nursing, and gathering information and experience with the latest equipment and systems in nursing, caregiving, and healthcare.

2. Graduate course

1) Gerontological Nursing I (S1; 2 credits)

The main theme of Gerontological Nursing I in 2022 was to understand the latest research related to the care of elderly persons and to discuss future perspectives in gerontological nursing from three viewpoints: basic biology, engineering, and clinical nursing research. Recent research papers were selected from these three fields and critically evaluated.

2) Gerontological Nursing II (A1; 2 credits)

Gerontological Nursing II provided lectures regarding recent topics around gerontological medicine and nursing from broad viewpoints, including biological, individual, and social aspects, by part-time lecturers and specialists from each research field. The aim of this course was to understand and learn scientific ways of thinking about gerontological considerations of the future Japanese community. The main titles in 2022 were as follows:

- a) Prevention of catheter failure using echo
- b) Nursing care innovation
- c) Biological nursing: skin blotting
- d) Nursing science and engineering for innovation of care in the super-aging society
- e) Care of cancer patients undergoing chemotherapy: Appearance care from the perspective of skin care
- f) Clinical issues and research findings in the community as a dermatology practitioner
- g) Clinical issues from a plastic surgery perspective with a focus on visiting physicians, and the latest wound care methods

3) Wound Care Management I (S2; 2 credits)

The main purpose of Wound Care Management I in 2022 was to learn and deepen understanding of the basic knowledge required to carry out wound nursing research, as well as to develop a broad interest in new knowledge and acquire an attitude and methodology for self-study. The topics were as follows:

- a) Prediction and prevention of wounds
- b) Assessment of wounds

c) Treatment and care of wounds

d) Institutions and policies related to wound care and management

4) Wound Care Management II (A2; 2 credits)

Wound management includes the prediction and prevention of wound development, wound assessment, treatment, and care (including excretory care), requiring a wide range of knowledge from nurses engaged in wound management. Therefore, research in wound care nursing requires a multidisciplinary approach that integrates different fields of nursing science and engineering. In this special lecture, students will learn the latest knowledge necessary for wound management, including basic research and practice, and will acquire scientific thinking ability and skills in wound nursing through discussions and exercises. Lectures, exercises, and discussions were held on (1) wound and skin assessment using equipment, and (2) pressure management and pressure injury prevention utilizing robotics technology.

5) Master's theses

The following research themes were submitted in 2022:

- “Development of e-learning and pelvic floor muscle contraction automatic evaluation algorithm for pelvic floor muscle training biofeedback using self-performed ultrasound”
- “Development of a skin temperature estimation system for a prediction method of pressure injury occurrence based on continuous body sensor data”
- “Development and evaluation of a rapid skin taurine measurement device using skin blotting for the early detection of dehydration”

6) Doctoral theses

The following research themes were submitted in 2022:

- “The effectiveness of local low-frequency vibration on wound healing of full-thickness wounds in a hyperglycemic rat model”
- “Predictive factors and characteristics of infusion site induration and subcutaneous edema among of the patients under outpatient chemotherapy” (in Japanese)
- “Identification of itch-prone skin in dry skin-derived

pruritus by detection of NGF/SEMA3A ratio”(in Japanese)

Research activities

1. Activity policy

Our gerontological nursing research focuses on those suffering from geriatric syndromes, such as pressure injuries, incontinence, malnutrition, pain, dysphagia and dementia. Our wound care management research focuses on pressure injuries, diabetic foot ulcers, and skin tears.

The majority of our clinical research has been conducted at The University of Tokyo Hospital. We regularly participate in pressure injury multi-disciplinary team rounds.

Regarding international activities, our department has been promoting collaborative research with researchers in universities around the world. Our counterparts include Curtin University (Australia) University of Nottingham, and Universitas Muhammadiyah Pontianak in 2022.

2. Research fields and themes in 2022

1) Basic experimental studies:

- Evaluation of wound condition using exudates
- Skin blotting for analyzing dehydration
- Cutaneous wound healing and diabetes mellitus
- Investigation of the effect of cellular senescence on wound healing
- Development of a novel method for controlling wound infection focusing on gene expression of bacteria and hosts

2) Nursing engineering:

- Sensing of the treatment environment and development of AI-based prediction models
- Non-invasive detection of tissue injury and pre-injury status using ultrasonography and thermography
- Development of apps using communication robots for the elderly
- Development of an absorbent pad for the prevention of incontinence-associated dermatitis
- Development of an educational system for new visiting nurses using XR technology

3) Clinical studies:

- Novel assessment technologies for pressure injuries

- Establishment of an automated pelvic floor muscle contraction evaluation method using ultrasonography
- Establishment of a novel assessment method for constipation using ultrasonography
- Implementation of ultrasonography-based peripheral venous catheter placement techniques
- Survey of the skin condition of wheelchair basketball athletes
- Survey on the relationship between the microbiota in the bed environment and the development of pressure injury infections
- Survey of the effectiveness of biofilm removal on wound healing
- Evaluation of the effectiveness of nurses who completed advanced nursing procedure training
- Development of a tele-nursing system and clinical evaluation of its effectiveness

Several awards were given for our research in 2022, as follows:

Presentations

- The 52nd Japanese Society for Wound Healing Research Encouragement Award (November 2022). Haba D, Qin Q, Minematsu T, Sanada H, Nakagami G. Verification of the effect of local low-frequency vibration stimulation on glucose metabolism and vasodilatation/neogenesis to promote healing of full-thickness wound in diabetic rats. (in Japanese)
- The Japanese Society of Physical Therapy 6th Symposium of Young Researchers Network Data Analysis Award (July 2022). Haba D, Qin Q, Nakagami G. New treatment strategy for diabetic foot ulcer based on promotion of glucose metabolism by local low-frequency vibration. (in Japanese)
- 31st Annual Meeting of the Japanese Society for Wound, Ostomy and Incontinence Management, Best Presentation Award, English Session (June 2022). Haba D, Nakagami G, Qin Q, Minematsu T, Sanada H. Local low-frequency vibration promotes wound healing of a full-thickness wound in the diabetic rat.

Papers

- 42nd Japan Academy of Nursing Science Academic Paper Award for Excellence (December 2022). Abe-Doi M, Murayama R, Kawamoto A,

- Komiyama C, Doorenbos A, Sanada H. Damage to subcutaneous tissue at the catheterization site during chemotherapy: A prospective observational study using ultrasonography. *Japan Journal of Nursing Science*. 2021;e12436.
- The 10th Society of Nursing Science and Technology Conference Award (October 2022). Higashimura S, Tamai N, Nakagami G, Tobe H, Sanada H. A pilot epidemiological study on chronic dehydration of older adults in a home care setting. *Journal of Nursing Science and Engineering*. 2022;9:123-135.
 - The 10th Society of Nursing Science and Engineering Incentive Award (October 2022). Matsumoto M, Ishibashi K, Kitamura A, Tamai N, Miura Y, Takahashi T, Higashimura S, Nakagami G, Sanada H. An AI-based evaluation method of fecal retention for rectal echocardiographic videos taken by home care nurses. *Journal of the Society of Nursing Science and Technology*. *Journal of Nursing Science and Engineering*. 2021;9:34-46. (in Japanese)
 - The 10th Society of Nursing Science and Technology Incentive Award (October 2022). Koudounas S, Minematsu T, Mugita Y, Tomida S, Nakai A, Nakagami G, Sanada H. Inhibiting effect of synthetic urine on the growth and mobility of *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabilis* and *Klebsiella pneumoniae* shifts to a promoting effect during culture. *Journal of Nursing Science and Engineering*. 2021;8:220-229.
 - Ohura Award of the Japanese Decubitus Ulcer Society (August 2022). Takizawa C, Kitamura A, Nakagami G, Matsumoto M, Hayashi C, Kawasaki A, Sanada H. The relationship between the temperature distribution detected by thermography and suspected deep tissue injuries. *Japanese Journal of Pressure Ulcers*. 2022;24(1):14-28.
 - Ohura Award of the Japanese Decubitus Ulcer Society (August 2022). Nakagami G, Yokota S, Kitamura A, Takahashi T, Morita K, Noguchi H, Ohe K, Sanada H. Supervised machine learning-based prediction for in-hospital pressure injury development using electronic health records: A retrospective observational cohort study in a university hospital in Japan. *International Journal of Nursing Studies*. 2021;119:103932.

References

Original Papers

1. Higashimura S, Tamai N, Nakagami G, Tobe H, Sanada H. A pilot epidemiological study on chronic dehydration of older adults in home care setting. *Journal of Nursing Science and Engineering*. 2022;9:123-135.
2. Matsumoto M, Misawa N, Tsuda M, Manabe N, Kessoku T, Tamai N, Kawamoto A, Sugama J, Tanaka AH, Haruma K, Sanada H, Nakajima A. Expert consensus document: diagnosis for chronic constipation with faecal retention in the rectum using ultrasonography. *Diagnostics*. 2022; 12(2):300.
3. Takahashi T, Nakagami G, Murayama R, Abe-Doi M, Matsumoto M, Sanada H. Automatic vein measurement by ultrasonography to prevent peripheral intravenous catheter failure for clinical practice using artificial intelligence: development and evaluation study of an automatic detection method based on deep learning. *BMJ open*. 2022; 12(e051466).
4. Higashimura S, Nakagami G, Sanada H. Effectiveness of new pelvic floor exercises on urinary incontinence in older women with cognitive impairment: A pilot study at long-term care facilities. *Journal of Society of Nursing Practice*. 2022;34(1):26-39.
5. Nitta S, Maeda T, Koudounas S, Minematsu T, Weller C, Sanada H. Which objective itch-assessment tools are applicable to patients with cognitive impairments? A scoping review. *International Journal of Older People Nursing*. 2022:e12458.
6. Tanabe H, Oosawa K, Miura M, Mizuno S, Yokota T, Ueda T, Zushi Y, Nagata M, Murayama R, Abe-Doi M, Sanada H. Effect of a thin-tipped short bevel needle for peripheral intravenous access on the compressive deformation and displacement of the vein: a preclinical study. *Journal of Vascular Access*. 2022: 11297298221075169.
7. Shintani Y, Murayama R, Abe-Doi M, Sanada H. Incidence, causes, and timing of peripheral intravenous catheter failure related to insertion timing in the treatment cycle in patients with

- hematological malignancies: a prospective descriptive study. *Japan Journal of Nursing Science*. 2022:e12484.
8. Sugama J, Ishibasi M, Ota E, Kamakura Y, Saitoh E, Sanada H, Nakayama T, Nomura T, Yamada M, Nakagami G, Sato N, Shibata S, Hase T, Fukada J, Miki T, Arita M, Urai T, Okawa Y, Kitamura A, Dai M, Takahashi T, Tamai N, Tobita I, Noguchi H, Matsumoto M, Miura Y, Mukai K, Mugita Y, Yoshida M, Kurachi M, Shirasaka T, Yamane Y. Japanese clinical practice guidelines for aspiration and pharyngeal residual assessment during eating and swallowing for nursing care. *Japan Journal of Nursing Science*. 2022:e12496.
 9. Murayama R, Oyama H, Abe-Doi M, Masamoto Y, Kashiwabara K, Tobe H, Komiyama C, Sanada H, Kurokawa M. Safety verification of a new peripheral intravenous catheter placed in the upper arm vein for administration of drugs with high irritant potential. *Drug Discoveries & Therapeutics*. 2022;16(3):128-134.
 10. Minematsu T, Tomida S, Tobe H, Koudaunas S, Nakagami G, Sanada H. Evaluation of liquid-less biofilm staining on wound blotting samples. *Journal of Nursing Science and Engineering*. 2022;9:222-228.
 11. Shimura T, Nakagami G, Ogawa R, Ono S, Takahashi T, Nagata M, Kashiwabara K, Sugama J, Sanada H, Oe M. Incidence of and risk factors for self-load-related and medical device-related pressure injuries in critically ill patients: a prospective observational cohort study. *Wound Repair and Regeneration*. 2022;30(4):453-467.
 12. Takizawa C, Kitamura A, Nakagami G, Matsumoto M, Hayashi C, Kawasaki A, Sanada H. The relationship between the temperature distribution detected by thermography and suspected deep tissue injuries. *Japanese Journal of Pressure Ulcers*. 2022;24(1):14-28.
 13. Qin Q, Nakagami G, Ohashi Y, Dai M, Sanada H, Oe M. Development of a self-monitoring tool for diabetic foot prevention using smartphone-based thermography: Plantar thermal pattern changes and usability in the home environment. *Drug discoveries & therapeutics*. 2022;16(4):169-176.
 14. Oe M, Fukuda M, Ohashi Y, Shimojima Y, Tsuruoka K, Qin Q, Yamauchi T, Sanada H. Evaluation of foot ulcer incidence in diabetic patients at a diabetic foot ulcer prevention clinic over a 10-year period. *Wound repair and regeneration*. 2022;30(5):546-552.
 15. Astrada A, Nakagami G, Fajrianita I, Matsumoto M, Kawamoto A, Jais S, Sanada H. Ultrasonographic features of diabetic foot osteomyelitis: a case series. *Journal of Wound Care*. 2022;31(9):748-754.
 16. Tsuruoka K, Oe M, Minematsu T, Tomida S, Ohashi Y, Shimojima Y, Qin Q, Abe M, Yamauchi T, Sanada H. Association between elevated skin temperature of the foot callus and inflammatory marker in people with diabetes. *Journal of Japanese Society of Wound, Ostomy and Continence Management*. 2022;23(3):261-268.
 17. Iwahira Y, Nakagami G, Sanada H. Risk factors for capsular contracture after breast reconstruction with tissue expanders and silicone implants in nonirradiated patients: A retrospective observational cohort study. *Medicine (Baltimore)*. 2022;101(48):e31837.
 18. Fact-finding Committee of the Japanese Society of Pressure Ulcers; Konya C, Takeuchi Y, Nakagami G, Kitamura A, Morita K, Ishizawa M, Abe Y, Higuchi H, Mizuki T, Motegi S, Shoji S, Shimada K, Tanaka K, Kawakami S, Sanada H. Nationwide time-series surveys of pressure ulcer prevalence in Japan. *Journal of Wound Care*. 2022;31(Sup12): S40-S47.

International Health

1. International Social Medicine

Department of Global Health Policy

Professor

Masahiro Hashizume, MD, PhD

Associate Professor

Chris Fook Sheng Ng, PhD

Assistant Professor

Paul Lester Chua, PhD, Vera Phung Ling Hui, PhD

Project Assistant Professor

Shuhe Nomura, PhD, Qiang Guo, PhD

Homepage <http://www.ghp.m.u-tokyo.ac.jp>

Introduction and Organization

As of March 2024 the department, headed by Professor Masahiro Hashizume, included the following staff complement; one associate professor (Chris Fook Sheng Ng); two assistant professors (Paul Lester Chua and Vera Phung Ling Hui); two project assistant professors (Shuhe Nomura and Qiang Guo); 2 post-doctoral fellows; 15 adjunct lecturers; 10 doctoral students; and 6 master's students.

The priority areas of research are:

- Health impacts of climate, climate change and air pollution.
- Health outcome research (mortality, morbidity and disability; health service research; health technology assessment and cost-effectiveness; disease modeling; and comparative risk factor analysis);
- Health system performance assessment, including the analysis of health system inputs, outputs, and impact;
- Health and foreign policy (e.g. global health architecture and governance, the G7 and global health, donor commitments, and innovations in global health).

Finally, the fundamental role of the department is to produce the next generations of leaders in global health.

Education

All lectures in the department are conducted in English, to ensure that student writing and presentation skills are held to an international standard.

Master's program

The Master's program is a demanding, inter-disciplinary program emphasizing student-directed learning, problem-solving, and the acquisition of fundamental public health skills required for global health practices (health policy, statistics, epidemiology, and social sciences). Students are required to complete a minimum of 30 course credits and a master's thesis. Beyond the program and concentration requirements, students are encouraged to consult with faculty advisers to choose elective courses best suited to their needs.

PhD program

The PhD program is designed to train the next

generation of leaders in global health. PhD students are required to complete a minimum of 24-course credits and a doctoral thesis which needs to be published in a peer-reviewed journal. PhD students without MPH degrees should take the lectures to acquire fundamental public health skills such as health policy, biostatistics and epidemiology.

Global Health Policy I and II

This course introduces the principles and theories of global health problems, as well as practical applications of quantitative methods (demography, statistics, epidemiology and econometrics) to analyze and interpret issues and challenges for policy.

The followings are the topics covered in the academic year 2022:

- Global environmental change and health
- Health impact assessments in environmental health
- Evidence synthesis for global health research
- Temperature and mortality
- Overview of global burden of disease
- Innovations in maternal and child health
- Planetary health
- Equity in health and universal health coverage assessment
- Data and epidemiological methods for environmental health research
- Air pollution and health
- Comparative risk assessment
- Cancer epidemiology and prevention GHP
- Infectious disease surveillance system
- Projections of climate change-related health impacts
- Environment and child health
- Japan's Global Health Diplomacy in the era of COVID-19 and beyond

GHP seminar

Every Tuesday, 13:00-15:00

1) Journal club

Students present a summary of research articles from the major medical, social science, economics journals, which are relevant to global health policy. The major objective is to share knowledge, evoke debates and facilitate discussions.

2) Research seminar

A guest speaker or a master or doctoral student presents his/her research. There is a 15-minute presentation-followed by a 30-minute discussion.

Research

Projections of excess mortality due to climate change - a multi-country environmental epidemiology study. Grant-in-Aid for Scientific Research (B) (Japan Society for the Promotion of Science) PI: Masahiro Hashizume

Climate Change and Human Health in Asia: Current Impacts, Future Risks, and Health Benefits of Mitigation Policies. E-Asia as part of Strategic International Collaborative Research Program (Japan Science and Technology Agency) PI: Masahiro Hashizume.

Human resource development and the development of infectious disease epidemiological methods for the expansion of infectious disease surveillance systems, including COVID-19. Health and Labour Science Research (Ministry of Health, Labour and Welfare) PI: Masahiro Hashizume.

Analysis of climate influences on medical conditions and diseases. Bilateral Collaborations (South Africa) (Japan Society for the Promotion of Science) Japanese PI: Masahiro Hashizume.

Use of burden of disease for health care research in the with/post-COVID-19 era and empirical analysis. Grant-in-Aid for Scientific Research (B) (Japan Society for the Promotion of Science) PI: Shuhei Nomura.

Selected Publications

1. Yamasaki L, Kamada T, Ng CFS, Takane Y, Nakajima K, Yamaguchi K, Oka K, Honda Y, Kim Y, Hashizume M. Heat-related mortality and ambulance transport after a power outage in the Tokyo metropolitan area. *Environ Epidemiol.* 2024 Feb 19;8(2):e292.
2. Mano Y, Yuan L, Ng CFS, Hashizume M*. Association between ambient temperature and

- genitourinary emergency ambulance dispatches in Japan: A nationwide case-crossover study. *Environ Epidemiol*. 2024 Feb 14;8(2):e298.
3. Sassa M, Yoneoka D, Ng CFS, Cao AQ, Devanathan G, Hashizume M, Nomura S. A comprehensive assessment of deworming coverage among pregnant women in low- and middle-income countries, 2000-30. *J Glob Health*. 2024 Mar 1;14:04002.
 4. Chen K, de Schrijver E, Sivaraj S, Sera F, Scovronick N, Jiang L, Roye D, Lavigne E, Kysely J, Urban A, Schneider A, Huber V, Madureira J, Mistry MN, Cvijanovic I; MCC Collaborative Research Network; Gasparrini A, Vicedo-Cabrera AM. Impact of population aging on future temperature-related mortality at different global warming levels. *Nat Commun*. 2024 Feb 27;15(1):1796.
 5. Htay ZW, Ng CFS, Kim Y, Lim YH, Iwagami M, Hashizume M. Associations between short-term exposure to ambient temperature and renal disease mortality in Japan during 1979-2019: A time-stratified case-crossover analysis. *Environ Epidemiol*. 2024 Feb 2;8(1):e293.
 6. Gao Y, Huang W, Zhao Q, Rytí N, Armstrong B, Gasparrini A, Tong S, Pascal M, Urban A, Zeka A, Lavigne E, Madureira J, Goodman P, Huber V, Forsberg B, Kysely J, Sera F, Guo Y, Li S; MCC Collaborative Research Network. Global, regional, and national burden of mortality associated with cold spells during 2000-19: a three-stage modelling study. *Lancet Planet Health*. 2024 Feb;8(2):e108-e116.
 7. Madaniyazi L, Armstrong B, Tobias A, Mistry MN, Bell ML, Urban A, Kysely J, Rytí N, Cvijanovic I, Ng CFS, Roye D, Vicedo-Cabrera AM, Tong S, Lavigne E, Íñiguez C, Silva SP, Madureira J, Jaakkola JJK, Sera F, Honda Y, Gasparrini A, Hashizume M, on behalf of the Multi-Country Multi-City Collaborative Research Network. Seasonality of mortality under climate change: a multicountry projection study. *Lancet Planet Health*. 2024 Feb;8(2): E86-E94.
 8. Kim Y, Oka K, Kawazu EC, Ng CFS, Seposo X, Ueda K, Hashizume M, Honda Y. Enhancing health resilience in Japan in a changing climate. *Lancet Reg Health West Pac*. 2023 Nov 15;40: 100970.
 9. Yuan L, Madaniyazi L, Vicedo-Cabrera AM, Honda Y, Ng CFS, Ueda K, Oka K, Tobias A, Hashizume M. A nationwide comparative analysis of temperature-related mortality and morbidity in Japan. *Environ Health Perspect*. 2023 Dec;131(12):127008.
 10. Thawonmas R, Hashizume M, Kim Y. Projections of temperature-related suicide under climate change scenarios in Japan. *Environ Health Perspect*. 2023 Nov;131(11):117012.
 11. Chua PLC, Takane Y, Ng CFS, Oka K, Honda Y, Kim Y, Hashizume M*. Net impact of air conditioning on heat-related mortality in Japanese cities. *Environ Int*. 2023 Nov;181: 108310.
 12. Nomura S, Nishio M, Abe SK, Eguchi A, Inoue M, Suzuki M, Hashizume M. Impact of the COVID-19 pandemic on cancer death locations in Japan: an analysis up to February 2023 on excess mortality. *J Epidemiol*. 2023 Oct 21. doi: 10.2188/jea.JE20230235.
 13. Liu C, Chen R, Sera F, Vicedo-Cabrera AM, Guo Y, Tong S, Lavigne E, Correa PM, Ortega NV, Achilleos S, Roye D, Jaakkola JJ, Rytí N, Pascal M, Schneider A, Breitner S, Entezari A, Mayvaneh F, Raz R, Honda Y, Hashizume M, Ng CFS, Gaio V, Madureira J, Holobaca IH, Tobias A, Íñiguez C, Guo YL, Pan SC, Masselot P, Bell ML, Zanobetti A, Schwartz J, Gasparrini A, Kan H. Interactive effects of ambient fine particulate matter and ozone on daily mortality in 372 cities: two stage time series analysis. *BMJ*. 2023 Oct 4;383:e075203.
 14. Yang Z, Huang W, McKenzie JE, Xu R, Yu P, Ye T, Wen B, Gasparrini A, Armstrong B, Tong S, Lavigne E, Madureira J, Kysely J, Guo Y, Li S; MCC Collaborative Research Network. Mortality risks associated with floods in 761 communities worldwide: time series study. *BMJ*. 2023 Oct 4;383:e075081.
 15. Huang W, Li S, Vogt T, Xu R, Tong S, Molina T, Masselot P, Gasparrini A, Armstrong B, Pascal M, Royé D, Sheng Ng CF, Vicedo-Cabrera AM, Schwartz J, Lavigne E, Kan H, Goodman P, Zeka A, Hashizume M, Diaz MH, De la Cruz Valencia

-
- C, Seposo X, Nunes B, Madureira J, Kim H, Lee W, Tobias A, Íñiguez C, Guo YL, Pan SC, Zanobetti A, Dang TN, Van Dung D, Geiger T, Otto C, Johnson A, Hales S, Yu P, Yang Z, Ritchie EA, Guo Y. Global short-term mortality risk and burden associated with tropical cyclones from 1980 to 2019: a multi-country time-series study. *Lancet Planet Health*. 2023 Aug;7(8):e694-e705.
16. He C, Chen R, Kim H, Hashizume M, Lee W, Honda Y, Kim SE, Guo YL, Schneider A, Ge W, Zhu Y, Zhou L, Kan H. Tropical cyclone and daily respiratory mortality across East Asia: a time series study. *Eur Respir J*. 2023 May 25: 2300546.
17. Kim SE, Hashizume M, Armstrong B, Gasparrini A, Oka K, Hijioka Y, Vicedo-Cabrera AM, Honda Y. Mortality risk of hot nights: a nationwide population-based retrospective study in Japan. *Environ Health Perspect*. 2023 May;131(5): 57005.

Department of Community and Global Health

Professor (cross-appointment)

Masahiro Hashizume, MD, PhD

Lecturer

Akira Shibamura, PhD

Assistant Professor

Junko Kiriya, PhD

Website: <http://www.ich.m.u-tokyo.ac.jp>

Introduction and Organization

The Department of Community and Global Health (formerly Department of International Community Health) has been headed by four professors since 1993: Professors Gen Ohi (1993-1996), Som-Arch Wongkhomthong (1996-1999), Susumu Wakai (1999-2006), and Masamine Jimba (2006-2023). Professor Masahiro Hashizume (Department of Global Health Policy) currently serves as Chief of the Department of Community and Global Health as a cross-appointment.

The mission of the department is to seek equity and social justice in health within and across nations. To achieve this, we aim toward:

1. Investigating how to improve health status of the most vulnerable people, in particular, in low- and middle-income countries
2. Undertaking research on the influence of globalization on health and social development
3. Investigating mechanisms to reduce health and development inequalities between and within nations

Our research focuses on how to promote community-based activities and how to link a bottom-up approach to national and international policies. As of March 2024, the department consists of the following members: the department chair and

professor, a lecturer, an assistant professor, three secretaries, 11 visiting lecturers, six doctoral students, six master's degree students, and 40 visiting scientists. More than half of the students in this department are international students.

International Cooperation Activities

We have been involved in international cooperation programs by Japan International Cooperation Agency (JICA). In the Training Course on Evidence-based Public Health Planning conducted by JICA Okinawa, we designed the evidence-based public health planning tool so that public health administrators from low- and middle-income countries can use it in the course. We have also participated in JICA's Ghana EMBRACE Implementation Research Project for the impact and implementation evaluations for the maternal, newborn, and child health program in Ghana, in collaboration with Ministry of Health and Ghana Health Service. We are also conducting an impact evaluation for Ghana's national rollout of the Maternal and Child Health Handbook.

Education

The main objectives of our teaching activities are the following two:

- 1) To train competent researchers who understand and complement the wise activities of practitioners in the field.
- 2) To train practitioners who can also wisely carry out research in the field.

The postgraduate curriculum is composed mainly of community and global health advanced courses, exercises and practical work. All curricula focus on community health. Our main educational activities other than the curriculum include technical assistance in writing Master's and doctoral theses. We always encourage students to publish their theses in international journals. In addition, we urge students to gain experiences in the field and learn about real global health from their experiences.

Because we have many international students, all lectures, practices, and discussions are carried out in English. For those who do not have health/medical background, we provide a wide variety of curricula from basics to advanced level.

We also provide training run by JICA and lectures at other universities to young leaders from overseas.

Research

The major objectives of our research activities are the following two:

- 1) To promote research which has a significant impact on international and local societies
- 2) To promote research which contributes to endogenous development

We aim to demonstrate research findings based on community-based data directly collected from the field. Therefore, we consider fieldwork very important. At the same time, our department aims to contribute to policy making and promoting actions for better health by making the most of community-based research. We carry out research by working in collaboration with different research institutes, international organizations, JICA, NGOs, and universities in low- and middle-income countries. We conduct research mainly in low- and middle-income countries, but we are also involved in research in Japan.

The major directions of current research have

encompassed 1) health, nutrition, and development, 2) health, human rights and human security, 3) ecological approach in infectious disease control, 4) health promotion, 5) disaster and health, 6) human resources for health worldwide, and 7) maternal and child health.

Our research has been conducted in various countries, including Nepal, Myanmar, Thailand, Viet Nam, Lao PDR, Cambodia, Indonesia, Ghana, Uganda, Malawi, and Zambia.

Publications

1. Kubota S, Ando M, Murray J, Khambounheuang S, Theppanya K, Nanthavong P, Tengbriacheu C, Sisavanh M, Khattiyod T, Asai D, Sobel H, Jimba M. A regulatory gap analysis of midwifery to deliver essential reproductive, maternal, newborn, child and adolescent health services in Lao People's Democratic Republic. *Lancet Reg Health West Pac.* 2023 Dec 5;43:100960. doi: 10.1016/j.lanwpc.2023.100960. eCollection 2024 Feb.
2. Jimba M, Long Sieber EN. Le pouvoir de la promotion de la santé de réduire la pauvreté à l'échelle mondiale. *Glob Health Promot.* 2023 Dec;30(4):58-61. doi: 10.1177/17579759231216059.
3. Jimba M, Long Sieber N. The power of health promotion to reduce poverty at the global level. *Glob Health Promot.* 2023 Dec;30(4):3-5. doi: 10.1177/17579759231213198.
4. Takeuchi H, Hasan SMT, Zaman K, Takanashi S, Hore SK, Yeasmin S, Ahmad SM, Alam MJ, Jimba M, Iwata T, Khan MA. Correction to: Impact of Haemophilus influenzae type b combination vaccination on asthma symptoms and pneumonia in 5-year-old children in rural Bangladesh: a longitudinal study and comparison with a previous cross-sectional study. *Respir Res.* 2023 Aug 24;24(1):210. doi: 10.1186/s12931-023-02502-6.
5. Koto-Shimada K, Carandang RR, Shibnuma A, Kiriya J, Ong KIC, Touch S, Koy V, Jimba M. Understanding competency of nursing students in the course of case-based learning in Cambodia: a convergent mixed method study. *BMC Nurs.*

- 2023 Aug 11;22(1):265. doi: 10.1186/s12912-023-01420-8.
6. Ikeda S, Shibamura A, Pokharel A, Silwal RC, Jimba M. Improving the quality of maternal and newborn healthcare at the district level: Addressing newborn deaths in Nepal. *PLOS Glob Public Health*. 2023 Aug 2;3(8):e0002101. doi: 10.1371/journal.pgph.0002101. eCollection 2023.
7. Mizukami A, Trinh MT, Hoang TP, Shibamura A, Ong KIC, Jimba M. Determinants of health-related quality of life among patients with systemic lupus erythematosus in Hanoi, Vietnam. *BMC Rheumatol*. 2023 Jun 22;7(1):16. doi: 10.1186/s41927-023-00339-6.
8. Nishikawa M, Yamanaka M, Shibamura A, Kiriya J, Jimba M. Japanese health and safety information for overseas visitors: a randomized controlled trial. *BMC Public Health*. 2023 Jun 21;23(1):1194. doi: 10.1186/s12889-023-16117-5.
9. Sarhan MBA, Fujiya R, Kiriya J, Htay ZW, Nakajima K, Fuse R, Wakabayashi N, Jimba M. Health literacy among adolescents and young adults in the Eastern Mediterranean region: a scoping review. *BMJ Open*. 2023 Jun 8;13(6):e072787. doi: 10.1136/bmjopen-2023-072787.
10. Tomita Y, Kiriya J, Silwal RC, Ong KIC, Shibamura A, Jimba M. Association between the person-centered maternity care experience and mental health after delivery in urban and rural Dhading, Nepal: a cross-sectional study. *BMC Pregnancy Childbirth*. 2023 May 30;23(1):398. doi: 10.1186/s12884-023-05709-z.
11. Pokharel A, Kiriya J, Shibamura A, Silwal RC, Jimba M. Association of workload and practice of respectful maternity care among the healthcare providers, before and during the early phase of COVID-19 pandemic in South Western Nepal: a cross-sectional study. *BMC Health Serv Res*. 2023 May 24;23(1):538. doi: 10.1186/s12913-023-09561-x.
12. Shahi PV, Shrestha RM, Schreinemachers P, Shibamura A, Kiriya J, Ong KIC, Jimba M. Identifying positive and negative deviants and factors associated with healthy dietary practices among young schoolchildren in Nepal: a mixed methods study. *BMC Nutr*. 2023 Mar 8;9(1):42. doi: 10.1186/s40795-023-00700-5.
13. Sapkota KP, Shibamura A, Ong KIC, Kiriya J, Jimba M. Accommodation and disability-specific differences in nutritional status of children with disabilities in Kathmandu, Nepal: A cross-sectional study. *BMC Public Health*. 2023 Feb 13;23(1):315. doi: 10.1186/s12889-023-14999-z.

International Health

2. International Biomedical Sciences

Department of Human Genetics

Professor

Akihiro Fujimoto, Ph.D.

Associate Professor

Motoko Unoki, PhD.

※The following information is the same as that of the previous year for certain reasons.

Homepage <http://www.humgenet.m.u-tokyo.ac.jp/index.en.html>

Introduction and Organization

The Department of Human Genetics was established in 1992. Currently, the department has 1 professor, 5 graduate student, and 1 undergraduate students. We also accept a few graduate students from other Universities for their PhD studies.

Teaching activities

For students at the Graduate School of International Health, courses that cover basic principles as well as the clinical application of human genetics are provided.

As to undergraduate students, a series of lectures is given to each of the sophomore (Human Genetics I, compulsory) and junior (Human Genetics II, elective) classes at the School of Health Sciences. A series of lectures is also provided to the first year (M0) students at the School of Medicine (compulsory).

Research activities

Human Genetics is a field focusing on the diversity of the human genome, and can include studies into the molecular mechanisms of genetics, evolutionary history of homo sapiens, cancer genome, as well as susceptibility genes for common and rare diseases. The findings of such genetic studies have proven useful in many applications, from supporting clinical diagnosis of diseases to drug development and therapy. Recent advancements in genomic analyses have allowed us to obtain enormous amounts of genetic and

transcriptomic data. Such data will continue to grow in size and utilization in society, reflecting the increasing importance of the field of human genetics.

Our department dives headlong into analyses of genomic, transcriptomic and epigenomic data to evaluate diversity in the human genome, as well as identifying variants and elucidating their functional importance and potential therapeutic applications. Our approach is holistic, focusing not only on data analysis, but also on practical experiments to reach our goal of uncovering new knowledge.

References

1. Yagasaki K, et al. Practical forensic use of kinship determination using high-density SNP profiling based on a microarray platform, focusing on low-quantity DNA. **Forensic Sci Int Genet.** 2022 Nov;61:102752
2. Kiyose H, et al. Comprehensive analysis of full-length transcripts reveals novel splicing abnormalities and oncogenic transcripts in liver cancer. **PLoS Genet.** 2022 Aug 4; 18(8): e1010342
3. Sano Y, et al. Likely pathogenic structural variants in genetically unsolved patients with retinitis pigmentosa revealed by long-read sequencing. **J Med Genet.** 2022 Nov;59(11): 1133-1138
4. Unoki M, Sasaki H: The UHRF protein family in epigenetics, development, and carcinogenesis (Review). **Proceedings of the Japanese Academy,**

Ser. B, Physical and Biological Science 98(8):
401-415, 2022

Department of Developmental Medical Sciences

Professor

Meng Ling Moi, Ph.D.

Assistant Professor

Misao Himeno, Ph.D.

Ryuji Majima, Ph.D.

Homepage <http://www.sih.m.u-tokyo.ac.jp/departments-en/>

Introduction and Organization

The Department of Maternal and Child Health was founded in 1966 as the first department that is dedicated to maternal and child health in Japan. With the subsequent expansion of research activities and the foundation of the Graduate School of Medicine, the department was renamed in 1998 as the Department of Developmental Medical Sciences. Of date, the department has been involved in basic science research and studies for the advancement of the physical and mental health of mothers and children. Basic science research includes those on the infection, immunity and metabolism, nervous and endocrine systems, whereas the epidemiologic studies deal with development, mother-to-child relationship, vaccination and health promotion. In 2021, under the new head of department and new staff members, the department has entered a new era, with emphasis than on pathogenesis, prevention and treatment of viral infections, child development specific conditions (congenital and acquired), from the standpoints of international health science, virology, immunology and neuroscience, with research and education goals for the development of measures that contributes to the improvement of maternal-child health and public health.

At present, our department consists of one professor, two assistant professors, two technical specialists, one secretary, eighteen invited lecturers, ten visiting researchers, and ten graduate students (including six

overseas student), one undergraduate student and four research students.

Our department offers courses to both undergraduate and postgraduate students, have weekly departmental meetings and individual research groups, communicate with collaborators inside or outside the University of Tokyo, and have seminars and meetings with researchers invited from abroad.

Currently, we are collaborating with academia and private research institutions from the Asia-Pacific regions, including China, Thailand, Viet Nam, Malaysia, Myanmar, Indonesia, Bangladesh, Sri Lanka and Australia, and the United States in research for the advancement of global maternal and children health. Our department are actively involved in the education and research with early and mid-career professionals, with aims of contributing to the upbringing of global leaders with competencies and skills to contribute to the fields of medical research and public health.

Teaching activities

1. Undergraduate course, Faculty of Medicine, School of Integrated Health Sciences
 - 1) Infectious diseases
 - 2) Immunity and defense mechanism
 - 3) Human growth and development
 - 4) Topics in life and environmental sciences
 - 5) Maternal and child health

- 6) School health
- 7) International health
- 8) Experiments in life sciences
- 9) Exercises in life sciences
- 10) Introduction to general health science

2. Graduate course, the Graduate School of Medicine, School of International Health

In addition to lectures and laboratory courses by our own staff, special lectures are given by experts both inside and outside the University.

Research activities

- (1) Mosquito-borne virus cohort studies in Vietnam, Thailand, Malaysia, the Philippines, Indonesia and Myanmar, our department conducts and research on viral and host-immunological factors that affects outbreaks.
- (2) Investigates the immunology and pathogenesis of arthropod-borne diseases infections by developing biological relevant in-vitro and in-vivo models. In collaboration with academic and industrial counterparts, our department also conducts studies on the development of diagnostics, vaccines and therapeutics for emerging and re-emerging infectious diseases including dengue, Zika, Chikungunya, Japanese encephalitis viruses.
- (3) Determination of the mechanisms of cross-reactive immunity during dengue, Zika, Japanese encephalitis and flavivirus secondary infection, with aims to determine the mechanisms behind pre-existing immunity in protection or pathogenesis and influences viral evolution during infection. This knowledge is critical for developing and deploying flavivirus vaccines and anti-viral therapeutics in an increasingly flavivirus-experienced world.
- (4) Clinical, genetic and pathologic studies of acute encephalopathy: Acute necrotizing encephalopathy, acute encephalopathy with biphasic seizures and late reduced diffusion, acute encephalitis with refractory, repetitive partial seizures, and clinically mild encephalitis/encephalopathy with a reversible splenial lesion.
- (5) International studies on the maternal and child health.
- (6) Studies on the virulence, drug resistance and vaccines for arthropod-borne diseases.
- (7) Molecular epidemiology of pediatric viral infections, in particular arthropod-borne diseases (dengue virus, zika virus, Japanese encephalitis virus).

References

1. Balingit JC, Dimamay MPS, Suzuki R, Matsuda M, Xayavong D, Ngwe Tun MM, Matias RR, Natividad FF, Moi ML, Takamatsu Y, Culleton R, Buerano CC, Morita K. Role of pre-existing immunity in driving the dengue virus serotype 2 genotype shift in the Philippines: A retrospective analysis of serological data. *Int J Infect Dis*. 2024 Feb;139:59-68. doi: 10.1016/j.ijid.2023.11.025.
2. Kobayashi D, Kai I, Faizah AN, Moi ML, Tajima S, Takasaki T, Sasaki T, Isawa H. Comparative analysis of the susceptibility of *Aedes aegypti* and Japanese *Aedes albopictus* to all dengue virus serotypes. *Trop Med Health*. 2023 Nov 2;51(1):61. doi: 10.1186/s41182-023-00553-5.
3. Haga K, Chen ZN, Himeno M, Majima R, Moi ML. Utility of an In-Vitro Micro-Neutralizing Test in Comparison to a Plaque Reduction Neutralization Test for Dengue Virus, Japanese Encephalitis Virus, and Zika Virus Serology and Drug Screening. *Pathogens*. 2023 Dec 20;13(1):8. doi: 10.3390/pathogens13010008.
4. Nguyen PHA, Fukushi S, Yamada S, Harada S, Yoshikawa T, Kinoshita H, Kawahara M, Ogawa T, Ebihara H, Moi ML, Saijo M. Analysis of antiviral drug properties of thymidine kinase of herpes B virus using recombinant herpes simplex virus 1. *Microbiol Spectr*. 2024 Jan 11;12(1):e0309123. doi: 10.1128/spectrum.03091-23.
5. Nakamura Y, Moi ML, Shiina T, Shin-I T, Suzuki R. Idiotope-Driven T-Cell/B-Cell Collaboration-Based T-Cell Epitope Prediction Using B-Cell Receptor Repertoire Sequences in Infectious Diseases. *Viruses*. 2023 May 17;15(5):1186. doi: 10.3390/v15051186.
6. Abeyagoonawardena H, Wijesinghe N, Navaratne V, Balasuriya A, Nguyen TTN, Moi ML, De Silva AD. Serological Evidence of *Zika virus* Circulation with Dengue and Chikungunya

- Infections in Sri Lanka from 2017. *J Glob Infect Dis.* 2023 Aug 30;15(3):113-120. doi: 10.4103/jgid.jgid_195_22.
7. Nguyen TTN, Choo EM, Nakamura Y, Suzuki R, Shiina T, Shin-I T, Fukuta M, Nguyen CT, Nguyen TTT, Nguyen LKH, Hoang VMP, Morita K, Dang DA, Hasebe F, Le TQM, Moi ML. Pre-existing cross-reactive neutralizing activity against SARS-CoV-2 and seasonal coronaviruses prior to the COVID-19 pandemic (2014-2019) with limited immunity against recent emerging SARS-CoV-2 variants, Vietnam. *Int J Infect Dis.* 2024 Feb;139:109-117. doi: 10.1016/j.ijid.2023.11.008.
 8. Phu Ly MH, Nguyen CT, Nguyen TV, Ngan Nguyen TT, Nabeshima T, Adungo F, Takamatsu Y, Huy NT, Mai Le TQ, Morita K, Hasebe F, Moi ML. Differential Infectivity of Human Neural Cell Lines by a Dengue Virus Serotype-3 Genotype-III Amino Acid Substitution Isolated from the Cerebrospinal Fluid of a Dengue Encephalitis Patient. *Can J Infect Dis Med Microbiol.* 2023 Jan 17;2023:2635383. doi: 10.1155/2023/2635383.
 9. Hoshino A, Takahashi N, Oka A, Mizuguchi M. Association of *IL6* and *IL10* gene promotor polymorphisms with susceptibility to acute necrotizing encephalopathy. *Front Neurosci.* 2023 Aug 3;17:1231957. doi: 10.3389/fnins.2023.1231957.
 10. Osawa T, Oya M, Okanishi T, Kuwatsuru R, Kawano H, Tomita Y, Niida Y, Nonomura N, Hatano T, Fujii Y, Mizuguchi M, Shinohara N. Clinical Practice Guidelines for tuberous sclerosis complex-associated renal angiomyolipoma by the Japanese Urological Association: Summary of the update. *Int J Urol.* 2023 Oct;30(10):808-817. doi: 10.1111/iju.15213.
 11. Sakuma H, Takanashi JI, Muramatsu K, Kondo H, Shiihara T, Suzuki M, Okanari K, Kasai M, Mitani O, Nakazawa T, Omata T, Shimoda K, Abe Y, Maegaki Y, Murayama K, Murofushi Y, Nagase H, Okumura A, Sakai Y, Tada H, Mizuguchi M; Japanese Pediatric Neuro-COVID-19 Study Group. Severe pediatric acute encephalopathy syndromes related to SARS-CoV-2. *FrontNeurosci.* 2023 Feb 27;17:1085082. doi: 10.3389/fnins.2023.1085082.
 12. 安西真衣, 大澤麻記, 水口雅. Canadian Occupational Performance Measure を用いた親子リハビリテーション入園の評価. *The Japanese Journal of Rehabilitation Medicine* 2023; 60(2): 152-158.
 13. Mizuguchi M, Shibata A, Kasai M, Hoshino A. Genetic and environmental risk factors of acute infection-triggered encephalopathy. *Front Neurosci.* 2023 Jan 24;17:1119708. doi: 10.3389/fnins.2023.1119708.
 14. Kashii H, Kasai S, Sato A, Hagino Y, Nishito Y, Kobayashi T, Hino O, Mizuguchi M, Ikeda K. Tsc2 mutation rather than Tsc1 mutation dominantly causes a social deficit in a mouse model of tuberous sclerosis complex. *Hum Genomics.* 2023 Feb 2;17(1):4. doi: 10.1186/s40246-023-00450-2.
 15. Murofushi Y, Sakuma H, Tada H, Mizuguchi M, Takanashi JI. Changes in the treatment of pediatric acute encephalopathy in Japan between 2015 and 2021: A national questionnaire-based survey. *Brain Dev.* 2023 Mar;45(3):153-160. doi: 10.1016/j.braindev.2022.10.008.
 16. Uematsu K, Matsumoto H, Zaha K, Mizuguchi M, Nonoyama S. Prediction and assessment of acute encephalopathy syndromes immediately after febrile status epilepticus. *Brain Dev.* 2023 Feb; 45(2):93-101. doi: 10.1016/j.braindev.2022.10.004.

Department of Human Ecology

Professor

Masahiro UMEZAKI, Ph.D.

Associate Professor

Shoko KONISHI, Ph.D.

Research Associates

Yuki MIZUNO, Ph.D.

Mihoko KIBE

Kyi Mar WAI, Ph.D.

Homepage: <http://www.humeco.m.u-tokyo.ac.jp/en/>

Introduction and Organization

The Department of Human Ecology was founded when Kenji Uraguchi was appointed Professor of the Human Ecology Department on April 1, 1965. Following Professor Uraguchi's retirement on March 31, 1966, Professor Haruo Katsunuma (also appointed Professor of the Public Health Department, School of Medicine) became a joint Professor of the Human Ecology Department. Tsuguyoshi Suzuki was appointed as an Associate Professor and worked in the Department until August 31, 1971, when he was transferred to the Faculty of Medicine, Tohoku University, as a Professor. After Professor Katsunuma left the Department on March 31, 1972, Professor Akira Koizumi became the head of the Human Ecology Department on April 1, 1972. Professor Koizumi was transferred to the Public Health Program, School of Medicine, on March 31, 1976, and Associate Professor Shosuke Suzuki served as a department head from April 1, 1976, to April 15, 1979.

Tsuguyoshi Suzuki was appointed Professor of the Human Ecology Program on April 16, 1979. He founded the theoretical framework of the current human ecology curriculum, which is based on studying the mechanisms by which humans adapt to the environment. After Associate Professor Shosuke Suzuki was transferred to the Faculty of Medicine, Gunma University, as Professor on July 31, 1981, Ryutaro Ohtsuka was appointed

Associate Professor on September 1, 1981. Associate Professor Ohtsuka established a methodology for collecting quantitative information on demography, nutrition, and subsistence, targeting small-scale populations based on extensive fieldwork, the methodology of which continues to be utilized by current department members. Following the retirement of Professor Tsuguyoshi Suzuki on March 31, 1992, Ryutaro Ohtsuka was appointed professor on April 1, 1992.

Chiho Watanabe was appointed as an Associate Professor in December 1997. He expanded methodologies that examine relations between the environment and health by utilizing various tools, such as measuring biomarkers in biological specimens collected in the field and animal experiments. Professor Ohtsuka retired on March 31, 2005, and Chiho Watanabe was appointed as a Professor on April 1, 2005. Masahiro Umezaki was appointed as an Associate Professor in August 2005. While relying on quantitative research based on fieldwork, he has also been exploring new research topics, including the application of spatial information sciences on health sciences, the roles of gut microbiota in human nutrition, mitigation/alleviation strategies of depopulation and aging in human populations, and medical anthropology. Professor Chiho Watanabe was transferred from the University of Tokyo to the National Institute of Environmental Studies on April 1, 2017. Masahiro Umezaki was appointed Professor as of January 1, 2018.

Shoko Konishi was appointed Associate Professor on June 1, 2018. Dr. Konishi has been studying the associations between fecundity, fertility, and environmental factors from the perspectives of population studies, environmental sciences, anthropology, and sociology.

In the fiscal year 2023, the Department had four faculty members: Professor Umezaki, Drs. Konishi, Mizuno, Wai, and Ms. Kibe. The Department also had 14 visiting lecturers for graduate and undergraduate courses. Professor Umezaki held additional roles in the Earth Observation Data Integration and Fusion Research Initiative (EDITORIA) at the University of Tokyo. Professor Umezaki and Dr. Konishi participated in the UTokyo Center for Climate Solutions (UTCCS).

Teaching activities

This Department is one of six in the School of International Health. Human Ecology Special Lecture I focuses on the basic components of human ecology, such as demography, nutrition, and environment, and introduces the notion of human ecosystems and low fertility in Japan. Human Ecology Special Lecture II emphasizes recent topics and ongoing research in human ecology and related areas. With these graduate student classes, we attempt to describe human ecology as a basic component of international health and provide current issues and the approaches used in this field. The graduate course lectures are provided in English.

The Department oversees a part of the School of Integrated Health Sciences, providing undergraduate course lectures on Human Ecology, Environment and Health, Demography, International Health, and Medical Anthropology. We are also responsible for organizing Pharmacology and Toxicology, Physiology, and Environmental and Human Engineering. We focus on introducing global-scale issues, such as population explosion, food security, and environmental issues, regarding problems faced by the Asia-Pacific region (including Japan). We also explore the relationship between human activities and environmental chemical contamination.

Research activities

Human ecology investigates the human population in the context of their respective ecologies and the global

context. Mostly, our research tackles tasks in the field of human environmental health and/or population ecology, but with a more comprehensive and broader context. Therefore, we must adopt different approaches, including fieldwork, experimentation, and geographic information system (GIS)/global positioning system (GPS) analyses. Our study fields include Asian-Oceanian (including Japan) rural and urban communities, focusing on population, nutrition, growth, the environment, and sustainability. Experimental studies have been conducted on the effects of perinatal exposure to heavy metals, emphasizing the factors that modify these effects. Almost all our studies require a transdisciplinary approach. We collaborate with various local and international research institutes. The following is a list of the major activities conducted in the past year:

1. Adaptation to low-protein diet

The inconsistency between the protein-deficient diets of Papua New Guinea highlanders and their muscular physique is well known. Moreover, although their protein intake is less than biologically adequate, disorders related to protein deficiency have rarely been reported. We speculate that the population has adapted to a low-protein diet by utilizing air nitrogen fixed by intestinal bacteria and/or by intensive “recycling” of the urea that passes into the gastrointestinal tract. Recent advances in sequencing techniques have enabled us to examine the adaptation of this population to a low-protein diet in a more direct way. We evaluated the gut microbiota of healthy individuals in four Papua New Guinea communities with varying degrees of protein deficiency. The association between the gut microbiota and variations in protein intake and nutritional biomarkers was investigated. Shotgun metagenomic analysis further demonstrated that some genes related to nitrogen fixation and urease were enriched in Papua New Guinea communities compared with other countries. Gnotobiotic animal experiments have revealed different nutritional responses to a low-protein diet depending on the type of gut microbiota transplanted.

2. Adaptive strategy to aging and depopulation

Japan is experiencing post-demographic transition (i.e., low fertility, aging, and population decrease). Targeting Japanese rural communities, the frontrunners

of this global issue, we conducted population projections and studies on their food habits, nutritional intake, and subjective perceptions of health. We also conducted a study to identify mitigation and alleviation strategies for aging and depopulation that have been formulated in local communities.

A case study in Nagasaki city, focusing on the residential zones on a steep slope and residents' aging, suggested that older people lived on steep slopes and without direct roadway access.

3. Nutrition and eating behaviors

Follow-up surveys have been conducted in a village in West Java, Indonesia. In the survey in 2022, the impact of COVID-19 epidemics on the survival strategies of the villagers was investigated.

We also performed animal experiments to elucidate the determinants of eating behavior. Our experiment revealed that mice preferred a high-fat diet to a high-carbohydrate diet after the consumption of soluble fiber for a certain period.

4. Interdisciplinary Investigation on the Technology, the Environment, and Fertility (IITEF)

Japan has the highest number of assisted reproductive technologies in the world. Our ongoing project is to test the hypothesis that exposure to technology and environmental chemicals is linked to increased infertility in the country. A total of 198 male participants were recruited from two hospitals in Tokyo and Tsukuba in 2020 and 2021. We analyzed associations between urinary isoflavone concentration and semen quality and sexual function of men seeking fertility treatment.

5. Health transition in Lao People's Democratic Republic

The diet in northern Laos can be characterized by a large consumption of rice and wild plants. Wild plants with bitter taste and astringency, which are supposed to contain more phytochemicals, are preferred by local people over cultivated vegetables. Phytochemicals are suspected to play a role in preventing non-communicable diseases such as cardiovascular diseases and hypertension. As people have gradually been involved in the market economy, they have started to consume more animal meat, oil and fat, and processed

foods with less consumption of wild plants and consequently phytochemicals. Our research project investigated the potential health impacts of such dietary changes in Oudomxay Province, northern Laos. The questionnaire survey and biological sample collection were conducted in five communities with different degrees of integration into the market economy. We sought to clarify a biological association between dietary transition and the recent emergence of noncommunicable diseases by evaluating oxidative stress, chronic inflammation, and gut microbiota composition. To examine phytochemical intake from wild plants, we have conducted quantitative dietary surveys, as well as identified species of wild edible plants and assessed their phytochemicals.

6. Potential fetal microbiome transfer from intrauterine exposure

Mounting evidence shows that bacteria in fertilization products (analyzed using DNA-based technologies) challenges the sterile womb hypothesis. We conducted cultivation-based and 16S rRNA sequence analyses using a mouse model of mid- and late gestation, which suggested the presence of bacteria in fetal, placental, and uterine tissues. This low-abundance fetal microbiome appears to be volatile and transient in nature, contrasting the relatively stable bacterial composition that matures during infancy. The similarity between the bacterial compositions of maternal and fetal tissues suggests vertical transmission, which has also been previously described in other animals and germ-free animal models. The existence of this fetal microbiome is hypothesized to be associated with immunocompetence in mothers and the development of immunity in fetuses. We have published a review article on fetal microbiomes.

7. Determinants of chronic inflammation in rural populations in Japan

Chronic inflammation is linked to various noncommunicable diseases and controlling it can improve health among older people. Various factors (e.g., age, diet, chemical exposure, etc.) have been reported as associated with chronic inflammation, but a complete picture of the determinants of chronic inflammation has not yet been clarified. We conducted a study to assess chronic inflammation and investigate

its determinants among residents in rural areas in Japan (Ojika in Nagasaki prefecture and Suzu in Ishikawa prefecture), where the population aging rate is high. Nutrient intake was assessed using a food frequency questionnaire, and several biomarkers were measured to assess chronic inflammation and trace element exposure.

8. Telomere Length and Successful Aging

Telomeres are repetitive oligomer sequences at the end of chromosomal DNA. Telomere length (TL) has been proposed as a biomarker of biological aging. TL shortening is associated with many pathophysiological outcomes later in life. On the other hand, the positive deviance (PD) concept is idealized for improving public health locally, as the whole community can adopt a healthy lifestyle structured on those of peers who have achieved better health against the odds, using locally assessable resources. Several previous studies have proved the success of PD in preventing and improving many major health burdens. This study assumes PDs are individuals with a longer TL compared to their peers in a similar condition. Our study identified the PD characteristics that have the potential to prevent biological aging among the general Japanese population. By understanding the PD characteristics, mitigating premature TL shortening would help combat the potential health risk before it gives rise to a significant health hazard.

9. Prenatal Environment And Child Health in Tak Province, Thailand, Tak_Peach Study

The early-life environment is a critical window that can determine the individual's health later in life. Meanwhile, the initial setting of telomere length (TL) played an important role in determining the health of the latter life. TL shortening is associated with several health outcomes and all-cause mortality. On the other hand, many factors, such as smoking, psychosocial stress, intestinal infection, and environmental factors, could lead to oxidative stress, accelerating TL shortening. We conducted a birth cohort study in Tak-province, Thailand, with the aims of 1) identifying the associations between prenatal exposure to environmental pollutants, psychosocial stress, and birth outcomes and TL in newborns; 2) identifying the exposure trend during prenatal and postnatal at the

follow-up time points; and 3) identifying the associations between pollutants and stress-induced telomere attrition and health outcomes of infants at the 2-months and 6-months follow-ups.

References

1. 今井 秀樹, 水野 佑紀, Cindy Rahman AISYAH, 増田 桃佳, 小西 祥子. (2023). 化学物質の複合曝露による健康影響の新しい評価方法とその課題. *日本衛生学雑誌* 78: 22009.
2. Wai KM, Swe T, Myar MT, Aisyah CR, Hninn TSS. (2023). Telomeres susceptibility to environmental arsenic exposure: Shortening or lengthening? *Front Public Health*. 2023 Jan 10;10:1059248.
3. Mizuno Y, Inaba Y, Masuoka H, Kibe M, Kosaka S, Natsuhara K, Hirayama K, Inthavong N, Kounnavong S, Tomita S, & Umezaki M. (2023). Impact of modernization on oxidative stress among indigenous populations in northern Laos. *American Journal of Biological Anthropology*, 181:352–363.
4. Leyso NL, Umezaki M. (2023) Uncovering spatial patterns and temporal trends in the ageing of the Tokyo Metropolis population. *Journal of Population Ageing* 16, 939–958.
5. Mizuno Y, Inaba Y, Masuoka H, Kibe M, Kosaka S, Natsuhara K, Hirayama K, Inthavong N, Kounnavong S, Tomita S, Umezaki M. (2023). Determinants of oxidative stress among indigenous populations in Northern Laos: trace element exposures and dietary patterns. *Science of the Total Environment*. 868, 161516.
6. Kosaka S, Suda K, Gunawan B, Umezaki, M. (2023). A questionnaire survey to assess motivations for food intake in Sundanese communities in Indonesia, and an assessment of the applicability of the questionnaire. *Japanese Journal of Health and Human Ecology* 89, 171–183.
7. Uchida M, Iwamoto T, Yamasaki K, Kariya F, Konishi S. (2023). The ratio of 2nd to 4th digit length and reproductive function of infertile male patients. *Reprod Med Biol*. 22(1) e12500.
8. Ohnishi M, Nakao R, Kawasaki R, Tanaka J, Kosaka S, Umezaki M. (2023). Factors associated with failure to receive health check-ups in Nagasaki Prefecture, Japan. *Journal of Rural Medicine*, 18(1), 28-35.

Department of Biomedical Chemistry

Professor

Tomoyoshi Nozaki, Ph.D., MD

Associate Professor

Yoh-ichi Watanabe, Ph.D.

Assistant Professor

Jeelani Ghulam, Ph.D., Santos Herbert Jimenez, Ph.D.

※The following information is the same as that of the previous year for certain reasons.

Homepage <http://www.biomedchem.m.u-tokyo.ac.jp/>

Introduction and Organization

Aim of our department is to contribute to global health and welfare from basic research. Our department, formerly named Biochemistry and Nutrition was renamed on April 1st, 1996 to The Department of Biomedical Chemistry as newly affiliating with Biomedical Science Division of International Health, Graduate School of Medicine, The University of Tokyo. Former Prof. Kiyoshi Kita (Professor Emeritus) has been retired in March 2016, and Dr. Tomoyoshi Nozaki, National Institute of Infectious Diseases, has been assigned as a new professor in October, 2016, and became a full-time processor in August, 2017.

Teaching activities

Teaching activities in our department cover a broad spectrum of biochemistry-oriented life sciences from premise to frontiers and in either conceptual or experimental point of view

Graduate Course: Biomedical Chemistry I, II

This course is comprised of lectures and seminars to provide basic concepts and newer vistas for understanding biomedical chemistry with special reference

to biochemistry and molecular biology. These include the structure and function of biomolecules, metabolism, its regulation, and underlying mechanism at either molecular, cellular and systemic level.

Undergraduate Course: Basic Life Science, Life Science and Genome Science I & II, Nutrition, Laboratory Practice for Life Science I & II, Seminar in Environmental and Human Life Sciences, Microbiology II (Parasitology).

Research activities

Our major research interests include virulence mechanisms and metabolism of protozoa, particularly *Plasmodium* spp. causing malaria and *Entamoeba histolytica* causing amebic dysentery. We mainly focus on vesicular trafficking, phagocytosis, autophagy, proteases, amino acid metabolisms, RNA maturation, translation, drug development, and organellogenesis. Our research approaches are very robust, and include biochemistry, molecular and cell biology, live imaging, multi-omics including metabolomics, and reverse genetics. Our present research themes include:

- Molecular elucidation of pathogenesis of parasites
- Biochemical and biological analyses of metabolism and organelles unique to parasites

- Analysis of vesicular traffic, protein secretion, and phagocytosis/trogocytosis in parasites
- Genome wide analysis and comparison of parasite strains
- Drug discovery and development against protozoan infections such as malaria and amebiasis
- Elucidation of divergence of RNA maturation and translation

References

1. Iwasaki, A., Ohtomo, K., Kurisawa, N., Shiota, I., Rahmawati, Y., Jeelani, G., Nozaki, T., Suenaga, K. Isolation, structure determination and total synthesis of Hoshinoamide C, an anti-parasitic lipopeptide from the marine cyanobacterium *Caldora penicillata*. *J Nat Prod.* 84:126-135, 2021. doi: 10.1021/acs.jnatprod.0c01209.
2. Pramisandi, A., Kurnia, K., Chrisnayanti, E., Bernawati, P., Dobashi, K., Mori, M., Mahsunah, A. H., Nonaka, K., Matsumoto, A., Kristiningrum, Hidayati, D. N., Dewi, D., Prabandari, E. E., Amalia, E., Nurkanto, A., Inaoka, D. K., Waluyo, D., Kita, K., Nozaki, T., Ōmura, S., Shiomi, K. Gentisyl alcohol and homogentisic acid: *Plasmodium falciparum* dihydroorotate dehydrogenase inhibitors isolated from fungi. *J. Gen. Appl. Microbiol.*, 67, 114-117, 2021. doi 10.2323/jgam.2020.08.004
3. Taku, I., Hirai, T., Makiuchi, T., Shinzawa, N., Iwanaga, S., Annoura, T., Nagamune, K., Nozaki, T., Saito-Nakano, Y. Rab5b-associated Arf1 GTPase regulates export of N-myristoylated adenylate kinase 2 from the endoplasmic reticulum in *Plasmodium falciparum*. *Front Cell Inf Microbiol* 10:610200, 2021. doi: 10.3389/fcimb.2020.610200..
4. Saito-Nakano, Y., Wahyuni, R., Nakada-Tsukui, K., Tomii, K., Mitra, B. N., Nozaki, T. Rab7D small GTPase is involved in phago-, trogocytosis and cytoskeletal reorganization in the enteric protozoan *Entamoeba histolytica*. *Cell. Microbiol.* 232, e13267, 2021. doi.org/10.1111/cmi.13267
5. Jeelani, G., Nozaki, T. Eukaryotic translation initiation factor 5A and its hypusination play an important role in proliferation and potentially in differentiation of the human enteric protozoan parasite *Entamoeba histolytica*. *PLoS Pathog.*, 17(2):e1008909, 2021. doi: 10.1371/journal.ppat.1008909.
6. Nurkanto, A., Jeelani, G., Santos, H. J., Mori, M., Annoura, T., Tozawa, Y., Shiomi, K., Nozaki, T. Characterization of *Plasmodium falciparum* pantothenate kinase and identification of its inhibitors from microbial natural products. *Front Cell Inf Microbiol.* 11:639065, 2021. doi: 10.3389/fcimb.2021.639065
7. Watanabe, N., Nakada-Tsukui, K., and Nozaki, T. Diversity of phosphoinositide binding proteins in *Entamoeba histolytica*. *Parasitol Int (review)* 83: 102367, 2021. doi: 10.1016/j.parint.2021.102367.
8. Das, K., Watanabe, N., and Nozaki, T. Two StAR-related lipid transfer proteins play specific roles in endocytosis, exocytosis, and motility in the parasitic protist *Entamoeba histolytica*. *PLoS Pathog*, 17(4): e1009551, 2021. doi: 10.1371/journal.ppat.1009551.
9. Das, K., Sardar, S., Ghosal, A., Saito-Nakano, Y., Dutta, S., Nozaki, T., Ganguly, S. Multilocus sequence typing (MLST) of *Entamoeba histolytica* identifies a genetic marker associated with disease outcomes. *Parasitol Int* 83:102370, 2021. doi: 10.1016/j.parint.2021.102370..
10. Santos, H. J. and Nozaki, T. Interorganellar communication and membrane contact sites in protozoan parasites. *Parasitol Int (review)* 83: 102372, 2021. doi: 10.1016/j.parint.2021.102372
11. Hartuti, E. D., Sakura, T., Tagod, M. S. O., Yoshida, E., Wang, X., Mochizuki, K., Acharjee, R., Matsuo, Y., Tokumasu, T., Mori, M., Waluyo, D., Shiomi, K., Nozaki, T., Hamano, S., Shiba, T., Kita, K., Inaoka, D., K. Identification of 3,4-dihydro-2H,6H-pyrimido[1,2-c][1,3]benzothiazin-6-imine derivatives as novel selective inhibitors of *Plasmodium falciparum* dihydro-orotate dehydrogenase. *Int J Mol Sci* 22:7236, 2021. doi: 10.3390/ijms22137236.
12. Takahashi, H., Iwasaki, A., Kurisawa, N., Suzuki, R., Jeelani, G., Matsubara, T., Sato, T., Nozaki, T., Suenaga, K. Motobamide, an antitrypanosomal cyclic peptide from the marine cyanobacterium *Leptolyngbya* sp. *J Nat Prod.* 84:1649-1655, 2021. doi: 10.1021/acs.jnatprod.1c00234.

13. Kurisawa, N., Otomo, K., Iwasaki, A., Jeelani, G., Nozaki, T., and Suenaga, K. Isolation and total synthesis of Kinenzoline, an antitrypanosomal linear depsipeptide isolated from a marine *Salileptolyngbya* sp. cyanobacterium. *J Org Chem*, 86(18):12528-12536, 2021. doi: 10.1021/acs.joc.1c00817.
14. Acharjee, R. Talaam, K. K., Hartuti, E. D., Matsuo, Y., Sakura, T., Gloria, B. M., Hidano, S., Kido, Y., Mori, M., Shiomi, K., Sekijima, M., Nozaki, T., Umeda, K., Nishikawa, Y., Hamano, S., Kita, K., Inaoka, D. K. Biochemical studies of mitochondrial malate:quinone oxidoreductase from *Toxoplasma gondii*. *Int J Mol Sci*. 22(15): 7830, 2021. doi: 10.3390/ijms22157830
15. Waluyo D, Prabandari EE, Pramisandi A, Hidayati DN, Chrisnayanti E, Puspitasari DJ, Dewi D, Suryani, Kristiningrum, Oktaviani AN, Afrianti KR, Nonaka K, Matsumoto A, Tokiwa T, Adipratiwi N, Ariyani T, Hartuti ED, Putri TZ, Rahmawati Y, Inaoka DK, Miyazaki Y, Sakura T, Nurlaila N, Siska E, Kurnia K, Bernawati P, Melinda M, Mahsunah AH, Nugroho NB, Mori M, Dobashi K, Yamashita M, Nurkanto A, Watanabe A, Shiomi K, Wibowo AE, Nozaki T. Exploring natural microbial resources for the discovery of anti-malarial compounds. *Parasitol Int*. 85:102432. doi: 10.1016/j.parint.2021.102432.
16. Ebihara, A., Iwasaki, A., Miura, Y., Jeelani, G., Nozaki, T., Suenaga, K. Isolation and total synthesis of Bromoiesol sulfates, anti-trypanosomal arylethers from a *Salileptolyngbya* sp. marine cyanobacterium. *J. Org. Chem*. 86(17):11763-11770, 2021. doi: 10.1021/acs.joc.1c01214.
17. Iwasaki, A., Teranuma, K., Kurisawa, N., Rahmawati, Y., Jeelani, G., Nozaki, T., Gerwick, W., Suenaga, K. First total synthesis and structure activity relationship of Iheyamide A, an anti-trypanosomal linear peptide isolated from a *Dapis* sp. marine cyanobacterium. *J. Nat. Prod*. 84(9):2587-2593, 2021. doi: 10.1021/acs.jnatprod.1c00792.
18. Nakada-Tsukui, K. and Nozaki, T. Trogocytosis in unicellular eukaryotes. Special Issue: New phase of phagocytosis and a bite of trogocytosis. *Cells*. 10(11), 2975, 2021. doi.org/10.3390/cells10112975
19. Bharadwaj, R., Tushar, Ahmad, A., Inampudi, K., Nozaki, T.*, Somlata*. An atypical EhGEF regulates phagocytosis in *Entamoeba histolytica* through EhRho1. *PLoS Pathog* 17(11):e1010030. (*double correspondence) doi: 10.1371/journal.ppat.1010030.
20. Peng, R., Yoshinari, S., Kawano-Sugaya, T., Jeelani, G., Nozaki, T. tRNA splicing in the unicellular parasitic amoebozoan: identification and functional characterization of divergent 3'-phosphate tRNA ligase from *Entamoeba histolytica*. *Front Cell Inf Microbiol*, section Parasite and Host, 11:746261, 2021. doi: 10.3389/fcimb.2021.746261.

School of Public Health

1. Epidemiology and Health Sciences

Department of Social and Preventive Epidemiology

Professor

Kentaro Murakami, Ph.D.

Homepage <https://www.nebn.m.u-tokyo.ac.jp/>

Introduction and Organization

The Department of Social and Preventive Epidemiology is a new department which was established at the same time of the establishment of the School of Public Health, the University of Tokyo (April 2007).

Epidemiology is a study of quantitatively assessing health status and disease development in populations and statistically analyzing the relationship of risk factors with the development of certain disease. In addition to traditional risk factors including alcohol drinking, smoking, nutrition, and physical activity, gene and factors controlling gene and socioeconomic factors are also important topics in epidemiologic research. Epidemiologic data are needed for conducting the assessment of certain treatment including medicine and estimating situation of disease development.

Epidemiology not only provides research methodology in the field of public health but also is considered a practical study for public health and thus a central field of health science. However, both education and research systems have long been insufficient in Japan. Social and preventive epidemiology is a study of epidemiologically clarifying the relationship between various phenomena in human society (including individual lifestyle) and certain disease.

The Department of Social and Preventive Epidemiology particularly focuses on nutrition, which is essential for individual and population health, as a main research topic and epidemiologically researches various issues related to nutrition (nutritional epidemiology), playing a central role in this research field in Japan.

The Department currently consists of one professor and one associate.

Teaching activities

We have the following two lectures in the School of Public Health.

Epidemiological research and practice
Practice and assessment in public health

Both are strongly associated with practical tasks in public health field, aiming at giving students opportunities for acquiring abilities of conducting public health activities and tasks based on theory of epidemiology.

We have also several lectures for students in other schools.

Research activities

Our main topic is basic research for development and application of research methodology in the field of nutritional epidemiology. Based on this basic research, we also conduct a wide range of epidemiologic research for investigating the relationship of nutrition with health and disease. As a characteristic of this research field, we conduct many multi-center studies with various kinds of disease.

Another characteristic is collection of research findings (scientific papers) derived from epidemiologic research all over the world on the association of nutrition with health and disease, which is applied for health control through nutrition improvement and disease control.

References

1. Sugimoto M, Murakami K, Sasaki S. Temporal patterns of sleep and eating among children during school closure in Japan due to COVID-19 pandemic: associations with lifestyle behaviours and dietary intake. *Public Health Nutr* 2023; 26(2): 393-407.
2. Murakami K, Shinozaki N, Livingstone MBE, Kimoto N, Masayasu S, Sasaki S. Relative validity of the online Meal-based Diet History Questionnaire for evaluating the overall diet quality and quality of each meal type in Japanese adults. *Br J Nutr* 2023; 130(4): 679-93.
3. Oono F, Murakami K, Fujiwara A, Shinozaki N, Adachi R, Asakura K, Masayasu S, Sasaki S. Development of a diet quality score for Japanese and comparison with existing diet quality scores regarding inadequacy of nutrient intake. *J Nutr* 2023; 153(3): 798-810.
4. Sugimoto M, Murakami K, Sasaki S. What happened among Japanese children from school closure due to COVID-19 after school re-opening? Changes in sleep habits and dietary intake. *J Nutr Sci* 2023; 12: e8.
5. Murakami K, Shinozaki N, Livingstone MBE, Kimoto N, Masayasu S, Sasaki S. Food combination questionnaire for Japanese: relative validity regarding food and nutrient intake and overall diet quality against the 4-day weighed dietary record. *J Nutr Sci* 2023; 12: e22.
6. Shinozaki N, Murakami K, Masayasu S, Sasaki S. Highly Processed Food Consumption and Its Association with Anthropometric, Sociodemographic, and Behavioral Characteristics in a Nationwide Sample of 2742 Japanese Adults: An Analysis Based on 8-Day Weighed Dietary Records. *Nutrients* 2023; 15(5): 1295.
7. Shinozaki N, Murakami K, Asakura K, Masayasu S, Sasaki S. Consumption of highly processed foods in relation to overall diet quality among Japanese adults: a nationwide study. *Public Health Nutr* 2023; 26(9): 1784-97.
8. Murakami K, Shinozaki N, Livingstone MBE, Yuan X, Tajima R, Matsumoto M, Masayasu S, Sasaki S. Associations of food choice values and food literacy with overall diet quality: a nationwide cross-sectional study in Japanese adults. *Br J Nutr* 2023; 130(10): 1795-1805.
9. Fujiwara A, Fukunaga A, Murakami K, Inoue Y, Nakagawa T, Yamamoto S, Konishi M, Mizoue T. Association between Dietary Hardness and Cognitive Dysfunction among Japanese Men in Their 60s: A Cross-Sectional Study. *Nutrients* 2023; 15(11): 2485.
10. Fujiwara A, Fukunaga A, Murakami K, Inoue Y, Nakagawa T, Yamamoto S, Konishi M, Mizoue T. Cross-Sectional Association between Estimated Hardness of the Habitual Diet and Depressive Symptoms in Older Japanese Men. *Nutrients* 2023; 15(13): 3034.
11. Murakami K, Shinozaki N, Kimoto N, Onodera H, Oono F, McCaffrey TA, Livingstone MBE, Okuhara T, Matsumoto M, Katagiri R, Ota E, Chiba T, Nishida Y, Sasaki S. Web-Based Content on Diet and Nutrition Written in Japanese : Infodemiology Study Based on Google Trends and Google Search. *JMIR FORMATIVE RESEARCH* 2023; 7(e47101): 1-17.
12. Oono F, Adachi R, Yaegashi A, Kishino M, Ogata R, Kinugawa A, Tsumura A, Suga M, Matsumoto M, Takaoka T, Kakutani Y, Murakami K, Sasaki S. Are popular books about diet and health written based on scientific evidence?: A comparison of citations between the US and Japan. *Public Health Nutr* 2023; 26: 2815-25.
13. Sugimoto M, Asakura K, Mori S, Shinozaki N, Murakami K, Imamura H, Nishiwaki Y. The nutritional characteristics of usual lunches consumed among Japanese workers: Comparison between different lunch type group. *J Occup Environ Med* 2023; 10.1097: 1-50.
14. Okada E, Nakade M, Hanzawa F, Murakami K, Matsumoto M, Sasaki S, Takimoto H. National Nutrition Surveys Applying Dietary Records or 24-h Dietary Recalls with Questionnaires: A Scoping Review. *Nutrients* 2023; 15(22): 4739.
15. Shinozaki N, Murakami K, Yuan X, Tajima R, Matsumoto M, Asakura K, Masayasu S, Sasaki S. The association of highly processed food consumption with food choice values and food literacy in Japanese adults: a nationwide cross-sectional study. *Int J Behav Nutr Phys Act* 2023; 20(1): 143.

16. Shinozaki N, Murakami K, Masayasu S, Sasaki S. Usual Nutrient Intake Distribution and Prevalence of Nutrient Intake Inadequacy among Japanese Children and Adults: A Nationwide Study Based on 8-Day Dietary Records. *Nutrients* 2023; 15(24): 5113.
17. Takezoe T, Murakami K, Fujishiro J, Horikawa M, Kubota M, Kanamori Y, Takahashi N, Nakano Y, Migita M, Matsufuji H, Sasaki S. Intake levels and main sources of nutrients for Japanese children with motor or intellectual disabilities. *J Nutr Sci* 2023; 12: e126.

Department of Clinical Epidemiology and Health Economics

Professor

Hideo Yasunaga, MD, PhD.

Assistant Professor

Hiroki Matsui, MPH.

Homepage <http://www.heer.m.u-tokyo.ac.jp/>

Introduction and Organization

The Department of Clinical Epidemiology and Health Economics was established in April 2007, as a part of Master of Public Health (MPH) program under the new School of Public Health (SPH). The Department is also affiliated with the Division of Social Medicine for doctoral education.

The mission of the Department is two folds; to help health professionals obtain scientifically sound basis and skills for evidence-based practice, and to empirically evaluate the clinical practice, health care system/policy for further improvement of the quality of health care. For this purpose, the Department puts a unique emphasis on quantitative analytic methods and inter-disciplinary theories across clinical epidemiology, health service research, health economics and health policy.

Teaching activities

Under the MPH program, the Department is responsible for 6 courses, one on introduction to clinical medicine for non-MD students, two on clinical epidemiology, two on health economics, and one on healthcare organization management.

The lecture course on clinical epidemiology provides a quick review on elementary to intermediate levels of epidemiology such as research design, bias and error,

and causal inference.

Health economics course provides an intermediate level of micro-economics and health economics theories of consumer choice, insurance, and human capital, and enhances discussion to apply these theories to behaviors of providers and consumers. The 3-day intensive course offers students an opportunity for hands-on training of actual cost-effectiveness analysis of health care and technologies.

Research activities

Current activities in this Department cover a broad range of health services research, including clinical epidemiological studies, economic evaluation of health technology and health policy, quality of life research, and hospital administration and quality assurance.

The Department also contributes to clinical and health service research using a large claim database based on the Japanese original patient classification system, Diagnosis Procedure Combination (DPC). DPC database allows a unique and detailed analysis on the process of care in acute care hospitals in this country. DPC database also provides resource diagnosis in hospital levels as well as regional levels, when combined with other public data sources such as the Patient Survey, and Hospital Census.

References

1. Akaba T, Jo T, Iwagami M, Hashimoto Y, Matsui H, Fushimi K, Tagaya E, Yasunaga H. Reduced asthma exacerbations in adult patients treated with bronchial thermoplasty. *Journal of Allergy and Clinical Immunology: In Practice*. 2023; 11(10):3076-3083.e3.
2. Amagasa S, Uematsu S, Kubota M, Kashiura M, Yasuda H, Hayakawa M, Yamakawa K, Endo A, Ogura T, Hirayama A, Yasunaga H, Tagami T. Relationship between institutional ventilated COVID-19 case volume and in-hospital death: A multicenter cohort study PLoS One. 2023;18(6): e0287310.
3. Aoki M, Aso S, Suzuki M, Tagami T, Sawada Y, Yasunaga H, Kitamura N, Oshima K; behalf of the SOS-KANTO 2017 Study Group. Association between obesity and neurological outcomes among out-of-hospital cardiac arrest patients: the SOS-KANTO 2017 study. *Resuscitation Plus*. 2023;17:100513.
4. Aso S, Ono S, Michihata N, Uemura K, Yasunaga H. Effectiveness of vaccination on influenza-related critical illnesses in the elderly population. *Journal of Infection and Chemotherapy*. 2023; 29(6):576-579.
5. Awano N, Jo T, Izumo T, Inomata M, Morita K, Matsui H, Fushimi K, Urushiyama H, Nagase T, Yasunaga H. Efficacy of initial high- versus low-dose intravenous corticosteroid therapy in patients with acute exacerbation of idiopathic interstitial pneumonia: A nationwide observational study. *Annals of Clinical Epidemiology*. 2023; 5(2):37-47.
6. Awano N, Jo T, Izumo T, Inomata M, Ito Y, Hashimoto Y, Matsui H, Fushimi K, Urushiyama H, Nagase T, Yasunaga H. Hospital volume and outcomes following bronchoscopy in patients with interstitial lung disease: A retrospective observational study using a national inpatient database in Japan. *Respiratory Investigation*. 2023;61(6):720-728.
7. Awano N, Jo T, Izumo T, Inomata M, Ito Y, Morita K, Matsui H, Fushimi K, Urushiyama H, Nagase T, Yasunaga H. Polymyxin B-immobilised fibre column treatment for acute exacerbation of idiopathic pulmonary fibrosis patients with mechanical ventilation: A nationwide observational study. *Journal of Intensive Care*. 2023;11(1):45.
8. Endo M, Jo T, Konishi T, Kumazawa R, Matsui H, Yasunaga H. Association between Legionella Urinary Antigen Tests on Admission and Inhospital Mortality in Patients with Atypical Pneumonia: A Nationwide Database Study. *International Journal of Mycobacteriology*. 2023; 12(3):350-356.
9. Fujiogi M, Konishi T, Michihata N, Hashimoto Y, Matsui H, Ishimaru T, Fushimi K, Yasunaga H, Fujishiro J. Perioperative outcomes of thyroid cancer surgery in children and adults: a nationwide inpatient database study in Japan. *Annals of Clinical Epidemiology*. 2023;5(1): 20-29.
10. Fujita A, Hashimoto Y, Matsui H, Yasunaga H, Aihara M. Recent trends in treatment and associated costs of primary angle-closure glaucoma: A Retrospective Cohort Study. *Ophthalmology Glaucoma*. 2023;6(3):308-315.
11. Fujita A, Sakata R, Hashimoto Y, Matsui H, Fushimi K, Yasunaga H, Aihara M. One-year costs of incisional glaucoma surgery and laser therapy. *Annals of Clinical Epidemiology*. 2023; 5(2):48-57.
12. Fujita A, Aoyama Y, Yamana H, Konishi T, Hashimoto Y, Aihara M, Yasunaga H. Validity of algorithms to identify patients with glaucoma using Japanese claims data. *Journal of Glaucoma*. 2023;32(4):307-312.
13. Fujita A, Hashimoto Y, Okada A, Matsui H, Yasunaga H, Aihara M. Practice patterns and costs of glaucoma treatment in Japan. *Japanese Journal of Ophthalmology*. 2023;67(5):590-601.
14. Fujita A, Hashimoto Y, Matsui H, Yasunaga H, Aihara M. Association between lifestyle habits and glaucoma incidence: a retrospective cohort study. *Eye*. 2023 ;37(16):3470-3476.
15. Hamada T, Michihata N, Saito T, Iwashita T, Shiomi H, Takenaka M, Matsui H, Fushimi K, Isayama H, Yasuda I, Yasunaga H, Nakai Y. Inverse association of hospital volume with in-hospital mortality rate of patients receiving endoscopic ultrasound-guided interventions for

- pancreatic fluid collections. *Gastrointest Endosc.* 2023;98(4):597-606.e2.
16. Hashimoto Y, Kaneko H, Aso S, Okada A, Matsui H, Yasunaga H, Aihara M, Obata R. Association between retinal vein occlusion and early-stage hypertension: a propensity score analysis using a large claims database. *Eye.* 2023 ;37(8):1741-1747.
17. Hashimoto Y, Yamana H, Iwagami M, Ono S, Takeuchi Y, Michihata N, Uemura K, Yasunaga H, Aihara M, Kaburaki T. Ocular adverse events after COVID-19 mRNA vaccination: matched cohort and self-controlled case series studies using a large database. *Ophthalmology.* 2023; 130(3):256-264.
18. Hashimoto Y, Okada A, Matsui H, Yasunaga H, Aihara M, Obata R. Recent trends in anti-vascular endothelial growth factor intravitreal injections: A large claims database study in Japan. *Japanese Journal of Ophthalmology.* 2023;67(1): 109-118.
19. Hattori Y, Tahara S, Aso S, Makito K, Matsui H, Fushimi K, Yasunaga H, Morita A. Comparison of Prophylactic Antibiotics for Endonasal Transsphenoidal Surgery Using a National Inpatient Database in Japan. *Journal of Antimicrobial Chemotherapy.* 2023;78(12):2909-2914.
20. Hayashi K, Sasabuchi Y, Matsui H, Nakajima M, Ohbe H, Fushimi K, Ono K, Yasunaga H. Additive effectiveness of acrylonitrile-co-methallyl sulfonate surface-treated membranes in treatment of pneumonia: A propensity score-matched retrospective cohort study. *Artificial Organs.* 2023 ;47(2):408-416.
21. Hayashi K, Sasabuchi Y, Matsui H, Nakajima M, Otawara M, Ohbe H, Fushimi K, Ono K, Yasunaga H. Does early excision or skin grafting of severe burns improve prognosis? A retrospective cohort study. *Burns.* 2023;49(3): 554-561.
22. Hidaka T, Ikawa F, Michihata N, Onishi S, Matsuda S, Ozono I, Oku S, Takayanagi S, Fushimi K, Yasunaga H, Kurisu K, Horie N. Perioperative Surgical Risks in Patients With Hemangioblastomas: A Retrospective Nationwide Review in Japan. *World Neurosurgery.* 2023;170: e21-e27.
23. Hikone M, Shibahashi K, Fukuda M, Shimoyama Y, Yamakawa K, Endo A, Hayakawa M, Ogura T, Hirayama A, Yasunaga H, Tagami T; J-RECOVER study group. Risk Factors Associated with Mortality among Mechanically Ventilated Patients with Coronavirus Disease 2019 Pneumonia: A Multicenter Cohort Study in Japan (J-RECOVER Study). *Internal Medicine.* 2023;62(15):2187-2194.
24. Hirano Y, Konishi T, Kaneko H, Itoh H, Matsuda S, Kawakubo H, Uda K, Matsui H, Fushimi K, Daiko H, Itano O, Yasunaga H, Kitagawa Y. Proportion of Early Extubation and Short-term Outcomes after Esophagectomy: A Retrospective Cohort Study. *International Journal of Surgery.* 2023;109(10):3097-3106.
25. Hirano Y, Konishi T, Kaneko H, Itoh H, Matsuda S, Kawakubo H, Uda K, Matsui H, Fushimi K, Daiko H, Itano O, Yasunaga H, Kitagawa Y. Early Postoperative Nonsteroidal Anti-inflammatory Drugs and Anastomotic Leakage After Oesophagectomy. *British Journal of Surgery.* 2023;110(2):260-266.
26. Hirano Y, Kaneko H, Konishi T, Itoh H, Matsuda S, Kawakubo H, Uda K, Matsui H, Fushimi K, Itano O, Yasunaga H, Kitagawa Y. Impact of Body Mass Index on Major Complications, Multiple Complications, In-hospital Mortality, and Failure to Rescue Following Esophagectomy for Esophageal Cancer: A Nationwide Inpatient Database Study in Japan. *Annals of Surgery.* 2023;277(4):e785-e792.
27. Hirano Y, Konishi T, Kaneko H, Itoh H, Matsuda S, Kawakubo H, Uda K, Matsui H, Fushimi K, Daiko H, Itano O, Yasunaga H, Kitagawa Y. Weight loss during neoadjuvant therapy and short-term outcomes after esophagectomy: A retrospective cohort study. *International Journal of Surgery.* 2023;109(4):805-812.
28. Hirano Y, Konishi T, Kaneko H, Itoh H, Matsuda S, Kawakubo H, Uda K, Matsui H, Fushimi K, Daiko H, Itano O, Yasunaga H, Kitagawa Y. Impact of prophylactic corticosteroid use on in-hospital mortality and respiratory failure after esophagectomy for esophageal cancer: Nationwide inpatient data study in Japan. *Annals*

- of Surgery. 2023;277(6):e1247-e1253.
29. Honda M, Yasunaga H, Michihata N, Miyakawa T, Kumazawa R, Matsui H, Imaizumi T. Impact of guideline recommendation for novel surgical procedures on surgeons' decisions: A time series analysis of gastric cancer surgeries from a nationwide cohort study. *International Journal of Surgery*. 2023;109(3):316-322.
 30. Honda A, Iizuka Y, Michihata N, Morita K, Mieda T, Takasawa E, Ishiwata S, Kakuta Y, Tomomatsu Y, Ito S, Inomata K, Matsui H, Fushimi K, Yasunaga H, Chikuda H. Risk factors for early mortality in elderly patients with unstable isolated C2 odontoid fracture treated with halo-vest or surgery. *Scientific Reports*. 2023;13(1):17962.
 31. Ichita C, Nakajima M, Ohbe H, Kaszynski RH, Sasaki A, Miyamoto Y, Kondo Y, Sasabuchi Y, Fushimi K, Matsui H, Yasunaga H. Effectiveness of early colonoscopy in patients with colonic diverticular hemorrhage: A nationwide inpatient analysis in Japan. *Digestive Endoscopy*. 2023; 35(4):520-528.
 32. Ishibashi T, Kaneko H, Matsuoka S, Suzuki Y, Ueno K, Ohno R, Okada A, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Node K, Yasunaga H, Komuro I. HDL cholesterol and clinical outcomes in diabetes mellitus. *Eur J Prev Cardiol*. 2023;30(8):646-653.
 33. Ishibashi T, Kaneko H, Ueno K, Morita K, Itoh H, Okada A, Kamiya K, Suzuki Y, Matsuoka S, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Ako J, Node K, Yasunaga H, Komuro I. Association between Early Initiation of Cardiac Rehabilitation and Short-Term Outcomes of Patients with Acute Heart Failure Admitted to Intensive Care Unit. *American Journal of Cardiology*. 2023;206:285-291.
 34. Ishimaru S, Michihata N, Kawamura Y, Uda K, Matsui H, Fushimi K, Yasunaga H, Yoshikawa T. Trend in the Numbers of Hospitalized Patients With Varicella, Herpes Zoster, and Ischemic Stroke in Japanese Individuals <20 Years of Age Before and After Implementation of Universal Varicella Vaccination. *Pediatr Infect Dis J*. 2023; 42(7):626-628.
 35. Ishimaru T, Shinjo D, Fujiogi M, Michihata N, Morita K, Hayashi K, Tachimori H, Kawashima H, Fujishiro J, Yasunaga H. Risk factors for postoperative anastomotic leakage after repair of esophageal atresia: a retrospective nationwide database study. *Surgery Today*. 2023;53(11): 1269-1274.
 36. Isogai T, Matsui H, Tanaka H, Makito K, Fushimi K, Yasunaga H. Incidence, management, and prognostic impact of arrhythmias in patients with Takotsubo syndrome: a nationwide retrospective cohort study. *European Heart Journal: Acute Cardiovascular Care*. 2023 ;12(12):834-846.
 37. Iwai C, Jo T, Konishi T, Fujita A, Michihata N, Matsui H, Fushimi K, Yasunaga H. Thrombotic risk of platinum combination chemotherapy with and without immune checkpoint inhibitors for advanced non-small cell lung cancer: a nationwide inpatient database study. *Cancer Immunology, Immunotherapy*. 2023;72(11):3581-3591.
 38. Iwai C, Jo T, Konishi T, Kumazawa R, Matsui H, Fushimi K, Yasunaga H. Comparative Safety and Effectiveness of Direct Oral Anticoagulants and Warfarin during Chemotherapy in Cancer Patients with Venous Thromboembolism Aged 75 Years or Older : A Nationwide Inpatient Database Study. *Gerontology*. 2023;69(5):561-570.
 39. Iwasaki Y, Ohbe H, Nakajima M, Sasabuchi Y, Ikumi S, Kaiho Y, Yamauchi M, Fushimi K, Yasunaga H. Association between intraoperative landiolol use and in-hospital mortality after coronary artery bypass grafting: A nationwide observational study in Japan. *Anesthesia & Analgesia*. 2023;137(6):1208-1215.
 40. Kameda S, Sasabuchi Y, Michihata N, Yamana H, Matsui H, Fushimi K, Yasunaga H, Kohro T. Prednisolone versus cyclosporine as initial treatment for Kawasaki disease. *Pediatrics International*. 2023;65(1):e15658.
 41. Kanazawa S, Kaneko H, Yano Y, Suzuki Y, Okada A, Matsuoka S, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Node K, Yasunaga H, Komuro I. Sex Differences in the Association between Hypertension and Incident Atrial Fibrillation. *JAHA*. 2023 ;12(5):e026240.
 42. Kamei J, Sugihara T, Yasunaga H, Matsui H, Sasabuchi Y, Fujimura T, Homma Y, Kume H.

- Impact of early ureteral drainage on mortality in obstructive pyelonephritis with urolithiasis: an analysis of the Japanese National Database. *World J Urol.* 2023;41(5):1365-1371.
43. Kaneko H, Yano Y, Okada A, Itoh H, Suzuki Y, Yokota I, Morita K, Fujiu K, Michihata N, Jo T, Yamaguchi S, Takeda N, Morita H, Node K, Yamauchi T, Nangaku M, Kadowaki T, McEvoy JW, Lam CSP, Yasunaga H, Komuro I. Age-Dependent Association between Modifiable Risk Factors and Incident Cardiovascular Disease. *Journal of the American Heart Association.* 2023; 12(2):e027684.
 44. Kaneko H, Yano Y, Lee H, Lee HH, Okada A, Suzuki Y, Itoh H, Matsuoka S, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Nishiyama A, Node K, Kim HC, Yasunaga H, Komuro I. Blood Pressure Classification Using the 2017 ACC/AHA Guideline and Heart Failure in 33,991 Cancer Patients. *Journal of Clinical Oncology.* 2023;41(5):980-990.
 45. Kimura Y, Jo T, Inoue N, Suzukawa M, Tanaka G, Kage H, Kumazawa R, Matsui H, Fushimi K, Yasunaga H, Matsui H. Association between systemic corticosteroid use and mortality in patients with epiglottitis. *Laryngoscope.* 2023; 133(2):344-349.
 46. Kitaoka H, Konishi T, Shitara Y, Ito A, Kashima K, Fujita A, Matsui H, Kato M, Takahashi N, Yasunaga H. Effects of milrinone on neonates after patent ductus arteriosus ligation: A retrospective nationwide database study. *Neonatology.* 2023 ;120(6):751-759.
 47. Kodama S, Jo T, Yasunaga H, Ohbe H, Michihata N, Matsui H, Okada A, Shirota Y, Fushimi K, Toda T, Hamada M. Perioperative use of intravenous levodopa as an anti-Parkinsonian drug: A propensity score analysis. *Movement Disorders Clinical Practice.* 2023 ;10(11):1650-1658.
 48. Konishi T, Tanabe M, Michihata N, Matsui H, Nishioka K, Fushimi K, Seto Y, Yasunaga H. Risk factors for arm lymphedema following breast cancer surgery: a Japanese nationwide database study of 84,022 patients. *Breast Cancer.* 2023;30(1):36-45.
 49. Konishi T, Ono S, Okada A, Matsui H, Tanabe M, Seto Y, Yasunaga H. Comparison of bleeding following gastrointestinal endoscopic biopsy in patients treated with and without direct oral anticoagulants. *Endoscopy International Open.* 2023;11(1):E52-E59.
 50. Konishi T, Sasabuchi Y, Matsui H, Tanabe M, Seto Y, Yasunaga H. Long-Term Risk of Being Bedridden in Elderly Patients Who Underwent Oncologic Surgery: A Retrospective Study Using a Japanese Claims Database. *Ann Surg Oncol.* 2023;30(8):4604-4612.
 51. Konishi M, Kaneko H, Itoh H, Matsuoka S, Okada A, Kamiya K, Sugimoto T, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Tamura K, Yasunaga H, Komuro I. Association of weight change and in-hospital mortality in patients with repeated hospitalization for heart failure. *J Cachexia Sarcopenia Muscle.* 2023;14(1):642-652.
 52. Konishi T, Fujiogi M, Sato M, Michihata N, Matsui H, Nishioka K, Tanabe M, Seto Y, Yasunaga H. Impact of the national action plan for antimicrobial resistance on antibiotic use for mastitis using a Japanese nationwide database. *Breast Care.* 2023;18(2):122-129.
 53. Kutsuna S, Ohbe H, Matsui H, Yasunaga H. Steroid pulse therapy for severe fever with thrombocytopenia syndrome patients may not improve prognosis: Retrospective analysis with overlap weighting using a national inpatient database. *Journal of Infection and Chemotherapy.* 2023;29(5):490-494.
 54. Matsumoto S, Tamiya H, Yamana H, Hosoi T, Matsui H, Fushimi K, Akishita M, Yasunaga H, Ogawa S. Association between the type of hypnotic drug and in-hospital fractures in older patients with neurocognitive disorders: A case-control study using a nationwide database. *Geriatr Gerontol Int.* 2023;23(7):500-505.
 55. Matsuo Y, Jo T, Makito K, Matsui H, Fushimi K, Yasunaga H. Association between use of transdermal tulobuterol and short-term outcomes in patients with stroke and underlying chronic obstructive pulmonary disease: a retrospective cohort study. *Medicine.* 2023;102(38):e35032.
 56. Miura S, Michihata N, Hashimoto Y, Matsui H, Fushimi K, Yasunaga H. Descriptive statistics

- and risk factor analysis of children with community-acquired septic shock. *Journal of Intensive Care*. 2023;11(1):6.
57. Miyachi H, Konishi T, Hashimoto Y, Matsui H, Fushimi K, Inozume T, Yasunaga H. Clinical course and outcomes of pemphigus vulgaris and foliaceus: a retrospective study using a nationwide database in Japan. *The Journal of Dermatology*. 2023;50(2):212-221.
 58. Miyachi H, Konishi T, Hashimoto Y, Matsui H, Fushimi K, Inozume T, Matsue H, Yasunaga H. Trends in mortality and morbidity in patients with bullous pemphigoid before and after approval of intravenous immunoglobulin in Japan: an interrupted time-series analysis. *Clin Exp Dermatol*. 2023;48(6):667-673.
 59. Miyakawa T, Michihata N, Kumazawa R, Matsui H, Honda M, Yasunaga H. Short-term surgical outcomes of laparoscopic and open surgery for rectal cancer: A nationwide retrospective analysis. *Asian Journal of Endoscopic Surgery*. 2023;16(3):376-385.
 60. Miyamoto Y, Ohbe H, Kumazawa R, Matsui H, Fushimi K, Yasunaga H, Ohta B. Evaluation of Plasmapheresis vs Immunoglobulin as First Treatment After Ineffective Systemic Corticosteroid Therapy for Patients With Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. *JAMA Dermatology*. 2023;159(5):481-487.
 61. Mizuno A, Kaneko H, Suzuki Y, Okada A, Takeda N, Morita H, Fujiu K, Node K, Yasunaga H, Komuro I. Enduring Relevance of the Stages of Change Model for Transforming Lifestyle Behaviors *Circ J*. 2023;87(8):1138-1142.
 62. Morita K, Fujiogi M, Michihata N, Matsui H, Fushimi K, Yasunaga H, Fujishiro J. Oral antibiotics and organ space infection after appendectomy and intravenous antibiotics therapy for complicated appendicitis in children. *European Journal of Pediatric Surgery*. 2023;33(1):74-80.
 63. Morita K, Matsui H, Ono S, Fushimi K, Yasunaga H. Association between better night-shift nurse staffing and surgical outcomes: a retrospective cohort study using a nationwide inpatient database in Japan. *Journal of Nursing Scholarship*. 2023 ;55(2):494-505.
 64. Morita K, Miyamoto Y, Mizuno A, Shirane S, Ohbe H, Hashimoto Y, Kaneko H, Matsui H, Fushimi K, Yasunaga H. Impact of a financial incentive scheme for team-based palliative care in patients with heart failure in Japan: A nationwide database study. *International Journal of Cardiology*. 2023;387:131145.
 65. Muramatsu K, Shigemi D, Honno K, Matsuoka M, Fujino Y, Yasunaga H, Unno N, Mitsuda N, Kimura T, Matsuda S. Hospital case volume and maternal adverse events following abnormal deliveries: Analysis using a Japanese National Inpatient Database. *International Journal of Gynecology and Obstetrics*. 2023;162(2):693-702.
 66. Murooka Y, Sasabuchi Y, Takazawa T, Matsui H, Yasunaga H, Saito S. Long-Term Prognosis Following Early Rehabilitation in the ICU: A Retrospective Cohort Study. *Crit Care Med*. 2023 Aug 1;51(8):1054-1063.
 67. Nishimoto Y, Ohbe H, Matsui H, Nakajima M, Sasabuchi Y, Sato Y, Watanabe T, Yamada T, Fukunami M, Yasunaga H. Effectiveness of systemic thrombolysis on clinical outcomes in high-risk pulmonary embolism patients with venoarterial extracorporeal membrane oxygenation: a nationwide inpatient database study. *Journal of Intensive Care*. 2023;11(1):4.
 68. Nishimoto Y, Ohbe H, Matsui H, Nakajima M, Sasabuchi Y, Sato Y, Watanabe T, Yamada T, Fukunami M, Yasunaga H. Trends in Treatment Patterns and Outcomes of Patients With Pulmonary Embolism in Japan, 2010 to 2020: A Nationwide Inpatient Database Study. *J Am Heart Assoc*. 2023;12(12):e028981.
 69. Nishimoto Y, Ohbe H, Matsui H, Nakata J, Takiguchi T, Nakajima M, Sasabuchi Y, Sato Y, Watanabe T, Yamada T, Fukunami M, Yasunaga H. Trends in Mechanical Circulatory Support Use and Outcomes of Patients With Cardiogenic Shock in Japan, 2010 to 2020 (from a Nationwide Inpatient Database Study). *Am J Cardiol*. 2023; 203:203-211.
 70. Ohbe H, Goto T, Okada A, Yasunaga H. Association between COVID-19 pandemic and mental disorders in spouses of intensive care unit

- patients: controlled interrupted time series study. *Intensive Care Medicine*. 2023;49(1):112-114.
71. Ohbe H, Sasabuchi Y, Iwagami M, Ogura T, Ono S, Matsui H, Yasunaga H. Intensive care unit versus high-dependency care unit for COVID-19 patients with invasive mechanical ventilation. *Annals of the American Thoracic Society*. 2023; 20(1):102-109.
 72. Ohbe H, Hachiya T, Yamaji T, Nakano S, Miyamoto Y, Sutoh Y, Otsuka-Yamasaki Y, Shimizu A, Yasunaga H, Sawada N, Inoue M, Tsugane S, Iwasaki M; Japan Public Health Center-based Prospective Study Group. Development and validation of genome-wide polygenic risk scores for predicting breast cancer incidence in Japanese females: a population-based case-cohort study. *Breast Cancer Research and Treatment*. 2023;197(3):661-671.
 73. Ohbe H, Ouchi K, Miyamoto Y, Ishigami Y, Matsui H, Yasunaga H, Sasabuchi Y. One-year functional outcomes after invasive mechanical ventilation for older adults with pre-existing long-term care needs. *Crit Care Med*. 2023;51(5): 584-593.
 74. Ohbe H, Nakajima M, Miyamoto Y, Shibahashi K, Matsui H, Yasunaga H, Sasabuchi Y. 1-year functional outcomes after cardiopulmonary resuscitation for older adults with pre-existing long-term care needs. *Age Ageing*. 2023;52(5): 1-9.
 75. Ohbe H, Sasabuchi Y, Doi K, Matsui H, Yasunaga H. Association Between Levels of Intensive Care and In-hospital Mortality in Patients Hospitalized for Sepsis Stratified by Sequential Organ Failure Assessment Scores. *Critical Care Medicine*. 2023;51(9):1138-1147.
 76. Ohbe H, Sasabuchi Y, Jo T, Michihata N, Matsui H, Yasunaga H. Kampo medicine in ICUs in Japan between 2010 and 2020. *Journal of Anesthesia*. 2023;37(4):654-656.
 77. Ohbe H, Tagami T, Endo A, Miyata S, Matsui H, Fushimi K, Kushimoto S, Yasunaga H. Trends in massive transfusion practice for trauma in Japan from 2011–2020: A nationwide inpatient database study. *Journal of Intensive Care*. 2023;11(1):46.
 78. Ohno R, Kaneko H, Ueno K, Kamiya K, Okada A, Suzuki Y, Matsuoka S, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Node K, Yasunaga H, Komuro I. Subjective Gait Speed and Risk of Developing Cardiovascular Events in 56,589 Cancer Survivors. *International Heart Journal*. 2023;64(4):672-677.
 79. Ohno R, Kaneko H, Ueno K, Aoki H, Okada A, Kamiya K, Suzuki Y, Matsuoka S, Fujiu K, Takeda N, Jo T, Ako J, Morita H, Node K, Yasunaga H, Komuro I. Association of Body Mass Index and Its Change with Incident Diabetes Mellitus. *J Clin Endocrinol Metab*. 2023;108(12):3145-3153.
 80. Ohno R, Kaneko H, Suzuki Y, Okada A, Matsuoka S, Ueno K, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Node K, Yasunaga H, Komuro I. Association of Metabolic Dysfunction Associated Fatty Liver Disease With Risk of HF and AF. *JACC Asia*. 2023;3(6):908-921.
 81. Okada A, Kaneko H, Matsuoka S, Itoh H, Suzuki Y, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Yamaguchi S, Node K, Yamauchi T, Yasunaga H, Komuro I. Association of cardiovascular health metrics with annual incidence of prediabetes or diabetes: Analysis of a nationwide real-world database. *Journal of Diabetes Investigation*. 2023;14(3):452-462.
 82. Okada A, Ikeda Kurakawa K, Harita Y, Shimizu A, Yamaguchi S, Aso S, Ono S, Hashimoto Y, Kumazawa R, Michihata N, Jo T, Matsui H, Fushimi K, Nangaku M, Yamauchi T, Yasunaga H, Kadowaki T. Comparison of Bleeding Complications after Pediatric Kidney Biopsy between Intravenous Sedation and General Anesthesia: A Nationwide Cohort Study. *BMC Pediatrics*. 2023;23(1):33.
 83. Okada A, Yamana H, Pan R, Yamaguchi S, Kumazawa R, Matsui H, Fushimi K, Honda Y, Nangaku M, Yamauchi T, Yasunaga H, Kadowaki T, Kim Y. Effect modification of the association between temperature variability and hospitalization for cardiovascular disease by comorbid diabetes mellitus: a nationwide time-stratified case-crossover analysis. *Diabetes Research and Clinical Practice*. 2023;202:110771
 84. Okada A, Honda A, Watanabe H, Sasabuchi Y, Aso S, Kurakawa KI, Nangaku M, Yamauchi T, Yasunaga H, Chikuda H, Kadowaki T,

- Yamaguchi S. Proteinuria screening and risk of bone fracture: a retrospective cohort study using a nationwide population-based database. *Clinical Kidney Journal*. 2023;17(1):1-9.
85. Okubo Y, Uda K, Miyairi I, Michihata N, Kumazawa R, Matsui H, Fushimi K, Yasunaga H. Nationwide epidemiology and clinical practice patterns of pediatric urinary tract infections: application of multivariate time-series clustering. *Pediatric Nephrology*. 2023;38(12):4033-4041.
 86. Okushin K, Yamana H, Tateishi R, Sato M, Tsutsumi T, Matsui H, Fushimi K, Yasunaga H, Koike K, Fujishiro M. Treatment and outcome of hepatorenal syndrome in Japan: a retrospective cohort study using a national inpatient database. *BMC Gastroenterol*. 2023;23(1):218.
 87. Ono S, Sasabuchi Y, Ishimaru M, Ono Y, Matsui H, Yasunaga H. Short-term effects of reduced cost sharing on childhood dental care utilization and dental caries prevention in Japan. *Community Dentistry and Oral Epidemiology*. 2023;51(2):228-235.
 88. Ono S, Michihata N, Yamana H, Uemura K, Ono Y, Jo T, Yasunaga H. Comparative effectiveness of BNT162b2 and mRNA-1273 booster dose after BNT162b2 primary vaccination against the Omicron variants: A retrospective cohort study using large-scale population-based registries in Japan. *Clinical Infectious Disease*. 2023;76(1):18-24.
 89. Pan R, Okada A, Yamana H, Yasunaga H, Kumazawa R, Matsui H, Fushimi K, Honda Y, Kim Y. Association between ambient temperature and cause-specific cardiovascular disease admissions in Japan: A nationwide study. *Environ Res*. 2023;225:115610.
 90. Saito K, Michihata N, Hamada T, Jo T, Matsui H, Fushimi K, Nakai Y, Yasunaga H, Fujishiro M. Gemcitabine plus nab-paclitaxel for pancreatic cancer and interstitial lung disease: A nationwide longitudinal study. *Cancer Sci*. 2023;114(10):3996-4005.
 91. Sato S, Yasunaga H. A Review of Studies Using Japanese Nationwide Administrative Claims Databases. *Annals of Clinical Epidemiology*. 2023;5(2):58-64.
 92. Setogawa N, Ohbe H, Matsui H, Yasunaga H. Amputation after endovascular therapy with and without intravascular ultrasound guidance: A nationwide propensity score matched study. *Circulation: Cardiovascular Interventions*. 2023;16(4):e012451.
 93. Shibahashi K, Ohbe H, Yasunaga H. Artificial cerebrospinal fluid use during burr-hole surgery and reoperation rate in patients with chronic subdural hematoma: an analysis using a nationwide inpatient database. *Acta Neurochirurgica*. 2023;165(5):1289-1296.
 94. Shibahashi K, Ohbe H, Matsui H, Yasunaga H. Real-world benefit of intracranial pressure monitoring in the management of severe traumatic brain injury: a propensity score matching analysis using a nationwide inpatient database. *Journal of Neurosurgery*. 2023;139(6):1514-1522.
 95. Shibahashi K, Ohbe H, Matsui H, Yasunaga H. Intracranial pressure monitoring in children with severe traumatic brain injury: a propensity score matching analysis using a nationwide inpatient database in Japan. *Neurosurgery*. 2023;94(1):99-107.
 96. Shigemi D, Okada A, Yasunaga H. Postoperative Adverse Events and Re-treatment among Patients who have undergone Laparoscopic and Robotic Sacrocolpopexy for Pelvic Organ Prolapse in Japan. *International Journal of Gynecology and Obstetrics*. 2023 ;161(1):114-119.
 97. Shigemi D, Yasunaga H. Association of white blood cell count after operative vaginal delivery with maternal adverse outcome: A retrospective cohort study. *Annals of Clinical Epidemiology*. 2023;5(4):113-120.
 98. Shimada K, Iwagami M, Makito K, Shigemi D, Uda K, Ishimaru M, Komiyama J, Morita K, Matsui H, Fushimi K, Yasunaga H, Tanaka M, Tamiya N. The Comparison of Caesarean Section Bleeding Between Volatile and Total Intravenous Anaesthesia in a Japanese Nationwide Database. *European Journal of Anaesthesiology and Intensive Care*. 2023;2(2):p e0021.
 99. Shinmoto K, Ohbe H, Nakajima M, Miyamoto Y, Sasabuchi Y, Yasunaga H, Hiraoka E. Outcomes after early versus delayed antibiotic treatment of liver abscess in Japan: A nationwide retrospective

- cohort study. *Journal of Infection and Chemotherapy*. 2023;29(1):1-6.
100. Shirata M, Ito I, Jo T, Iwao T, Oi I, Hamao N, Nishioka K, Yamana H, Nagase T, Yasunaga H, Hirai T. Factors Associated With the Development of Bacterial Pneumonia Related to Seasonal Influenza Virus Infection: A Study Using a Large-scale Health Insurance Claim Database. *Open Forum Infect Dis*. 2023;10(5):ofad222.
 101. Suzuki J, Endo S, Suzuki T, Sasahara T, Hatakeyama S, Morisawa Y, Hayakawa M, Yamakawa K, Endo A, Ogura T, Hirayama A, Yasunaga H, Tagami T. The effect of inhaled ciclesonide in non-critically ill hospitalized patients with COVID-19: a multicenter observational study in Japan. *Open Forum Infectious Diseases*. 2023 ;10(12):ofad571.
 102. Suzuki Y, Kaneko H, Tamura Y, Okada A, Fujiu K, Michihata N, Takeda N, Jo T, Morita H, Node K, Yasunaga H, Komuro I. Cardiovascular events after the initiation of immune checkpoint inhibitors. *Heliyon*. 2023;9(5):e16373.
 103. Suzuki Y, Kaneko H, Yano Y, Okada A, Hashimoto Y, Itoh H, Matsuoka S, Yokota I, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Kamiya K, Matsunaga A, Ako J, Node K, Yasunaga H, Komuro I. Threshold of body mass index for the development of hypertension among the Japanese adults. *Journal of Nutrition*. 2023; 152(11):2565-2571.
 104. Suzuki Y, Kaneko H, Yano Y, Okada A, Itoh H, Matsuoka S, Yokota I, Imaizumi T, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Node K, Yasunaga H, Komuro I. Interaction of Blood Pressure and Glycemic Status in Developing Cardiovascular Disease: Analysis of a Nationwide Real-World Database. *JAHA*. 2023; 12(1):e026192
 105. Suzuki Y, Kaneko H, Yano Y, Okada A, Fujiu K, Matsuoka S, Michihata N, Jo T, Takeda N, Morita H, Node K, Yasunaga H, Oparil S, Komuro I. The association of BP with cardiovascular outcomes in patients with dipstick proteinuria and preserved kidney function. *Hypertension Research*. 2023;46(4):856-867.
 106. Suzuki Y, Kaneko H, Tamura Y, Okada A, Michihata N, Jo T, Takeda N, Morita H, Fujiu K, Yasunaga H, Komuro I. Sex-Specific Differences in the Risk of Heart Failure following Anti-HER2 Monoclonal Antibody Therapy. *Oncology*. 2023;101(6):358-361.
 107. Suzuki Y, Kaneko H, Yano Y, Okada A, Matsuoka S, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Node K, Yasunaga H, Komuro I. Reduction in blood pressure for people with isolated diastolic hypertension and cardiovascular outcomes. *European Journal of Preventive Cardiology*. 2023;30(10):928-934.
 108. Tahara S, Hattori Y, Aso S, Uda K, Kumazawa R, Matsui H, Fushimi K, Yasunaga H, Morita A. Endoscopic Surgery versus Craniotomy for Spontaneous Intracerebral Hemorrhage in the Late Elderly Patients. *Journal of Stroke and Cerebrovascular Diseases*. 2023;32(11):107327.
 109. Tahara S, Hattori Y, Aso S, Uda K, Kumazawa R, Matsui H, Fushimi K, Yasunaga H, Morita A. Outcomes after Endoscopic Evacuation versus Evacuation Using Craniotomy or Stereotactic Aspiration for Spontaneous Intracerebral Hemorrhage: Analysis Using a Japanese Nationwide Database. *Neurocritical Care*. 2023; 38(3):667-675.
 110. Takamoto N, Konishi T, Fujiogi M, Kutsukake M, Morita K, Hashimoto Y, Matsui H, Fushimi K, Yasunaga H, Fujishiro J. Outcomes following laparoscopic versus open surgery for pediatric intussusception: Analysis using a national inpatient database in Japan. *Journal of Pediatric Surgery*. 2023;58(11):2255-2261.
 111. Uemura K, Kanata T, Ono S, Michihata N, Yasunaga H. The disease severity of COVID-19 caused by Omicron variants: A brief review. *Annals of Clinical Epidemiology*. 2023;5(2):31-36.
 112. Uemura K, Ono S, Michihata N, Yamana H, Yasunaga H. Duration of influenza vaccine effectiveness in the elderly in Japan: A retrospective cohort study using large-scale population-based registry data. *Vaccine*. 2023; 41(19):3092-3098.
 113. Ueno K, Kaneko H, Kamiya K, Okada A, Itoh H, Konishi M, Sugimoto T, Suzuki Y, Matsuoka S, Fujiu K, Michihata N, Jo T, Takeda N, Morita H,

- Ako J, Node K, Yasunaga H, Komuro I. Association of early acute-phase rehabilitation initiation on outcomes among patients aged ≥ 90 years with acute heart failure. *Journal of the American Geriatrics Society*. 2023;71(6):1840-1850.
114. Ueno K, Kaneko H, Kamiya K, Okada A, Suzuki Y, Fujii K, Matsuoka S, Michihata N, Takeda N, Jo T, Morita H, Ako J, Node K, Yasunaga H, Komuro I. Gait speed and cardiovascular disease by glycemic status. *American Journal of Preventive Medicine*. 2023 ;65(1):45-51.
 115. Ueno K, Kaneko H, Okada A, Suzuki Y, Matsuoka S, Fujii K, Michihata N, Jo T, Takeda N, Morita H, Kamiya K, Ako J, Node K, Yasunaga H, Komuro I. Association of four health behaviors in Life's Essential 8 with the incidence of hypertension and diabetes mellitus. *Preventive Medicine*. 2023;175:107685.
 116. Urata S, Michihata N, Inuzuka R, Matsui H, Fushimi K, Ishimaru M, Kato M, Yasunaga H. Factors affecting in-hospital mortality among pediatric patients with myocarditis treated with mechanical circulatory support. *J Cardiol*. 2023; 82(2):108-112.
 117. Watanabe H, Yamana H, Okada A, Matsui H, Fushimi K, Yasunaga H. Therapeutic plasma exchange for anti-glomerular basement membrane disease with dialysis-dependent kidney failure without diffuse alveolar hemorrhage. *Journal of Nephrology*. 2023;36(8): 2317-2325.
 118. Watanabe J, Sasabuchi Y, Ohbe H, Nakajima M, Matsui H, Miki A, Horie H, Kotani K, Yasunaga H, Sata N. Impact of preoperative stoma site marking on morbidity and mortality in patients with colorectal perforation: A nationwide retrospective cohort study. *World Journal of Surgery*. 2023;47(11):2857-2864.
 119. Yamada Y, Ohbe H, Yasunaga H, Nakamoto H, Miyakawa Y. Clinical characteristics, treatments, and outcomes of thrombotic thrombocytopenic purpura treated with plasma exchange in Japan: a nationwide inpatient database study. *Renal Replacement Therapy*. 2023;9:25.
 120. Yamamoto R, Tamura T, Haiden A, Yoshizawa J, Homma K, Kitamura N, Sugiyama K, Tagami T, Yasunaga H, Aso S, Takeda M, Sasaki J; SOS-KANTO 2017 Study Group. Frailty and Neurologic Outcomes of Patients Resuscitated From Nontraumatic Out-of-Hospital Cardiac Arrest: A Prospective Observational Study. *Ann Emerg Med*. 2023;82(1):84-93.
 121. Yamana H, Lee S, Lin YC, Yoon NH, Fushimi K, Yasunaga H, Cheng SH, Kim HS. Institutional Variance in Mortality after Percutaneous Coronary Intervention for Acute Myocardial Infarction in Korea, Japan, and Taiwan. *International Journal of Health Policy and Management*. 2023;12:6796.
 122. Yamana H, Ono S, Michihata N, Uemura K, Jo T, Yasunaga H. Effect of the 23-valent pneumococcal polysaccharide vaccine on the incidence of hospitalisation with pneumonia in adults aged ≥ 65 years: retrospective cohort study using a population-based database in Japan. *Clinical Microbiology and Infection*. 2023;29(7): 904-910.
 123. Yamana H, Konishi T, Yasunaga H. Validation studies of Japanese administrative health care data: A scoping review. *Pharmacoepidemiol Drug Saf*. 2023;32(7):705-717.
 124. Yamana H, Yamasaki K, Jo T, Yatsushashi H, Yasunaga H. A descriptive analysis of acute viral hepatitis using a database with electronic medical records and claims data. *Annals of Clinical Epidemiology*. 2023;5(4):107-112.
 125. Yamazaki R, Ohbe H, Matsuda Y, Kito S, Shigeta M, Morita K, Matsui H, Fushimi K, Yasunaga H. Effectiveness of medical fee revisions for psychotropic polypharmacy in patients with mood disorders in Japan: An interrupted time-series analysis using a nationwide inpatient database. *Asian J Psychiatr*. 2023;84:103581.
 126. Yokoyama A, Jo T, Sakamoto Y, Urushiyama H, Tamiya H, Tanaka G, Kumazawa R, Matsui H, Fushimi K, Yasunaga H, Nagase T. Effectiveness and safety of the co-administration of Yokukan-San (Japanese Herbal Medicine) with Antipsychotics in Hospitalized Older Patients with Pneumonia. *Geriatrics & Gerontology International*. 2023 ;23(11):849-854.
 127. Yoshiyasu N, Jo T, Sato M, Kumazawa R, Matsui H, Fushimi K, Nagase T, Yasunaga H, Nakajima J.

Readmissions and costs in cadaveric and living-donor lobar lung transplantation: Analysis using a national database. *JHLT Open*. 2023;2:100010

Department of Health Communication

Professor

Takahiro Kiuchi, M.D., Ph.D.

Associate Professor

Tsuyoshi Okuhara, Ph.D., MPH

Homepage <http://www.umin.ac.jp/hc/>

Introduction and Organization

The Department of Health Communication was established as a part of the newly developed School of Public Health (professional graduate school) in April 2007, which was derived from the University Hospital Medical Information Network (UMIN) Center. It consists of two faculty members: a professor and an associate professor.

Health communication is a major discipline in school of public health, especially in the US, and there are many graduate programs and research centers for health communication. On the other hand, there have been few such departments in Japan, although the importance of the health communication discipline has gradually been recognized among the academic society as well as among general public. Our department was established one of the few departments specialized in health communication in Japan.

Teaching Activities

The Department of Health Communication, within the School of Public Health, is a professional graduate program that aims to foster the development of medical and public health professionals as well as researchers. We strive to make the most of our professional activities and experience at UMIN Center. We provide lectures and practical instruction in the program. The following is the current curriculum:

[Health Communication Lectures]

1. Introduction to health communication
2. Evaluation and research in health communication
3. Media and communication (1): Television
4. Media and communication (2): News paper
5. Media and communication (3): Internet
6. Improving communication based on empirical research
7. Patient and public education
8. Communication with foreign patients
9. Communication for behavioral changes (1)
10. Communication for behavioral changes (1)
11. Risk communication and community engagement
12. Social marketing
13. Communication in group and organization
14. Group discussion

[Health Communication Practice]

1. Health writing (1) Creating a document to support patients and families.
2. Health writing (2) Creating a document to encourage behavior change
3. MBTI (Myers-Briggs Type Indicator) (1)(2)(3)
4. Mass communication: Media doctor
5. Coaching
6. Health writing (3) Presentation and discussion

[Medical research and CDISC standards]

1. Introduction to data management in clinical research
2. Introduction to CDISC standards

3. Standardization of case report form – CDASH
4. Data and metadata – Define.xml
5. Standardization of dataset for analysis – AdaM
6. Electronic application by CDISC standards
7. Standardization of data format – SDTM

In the undergraduate program, we present lectures entitled “Medical Literature Informatics” and “health communication.”

Research Activities

(1) Research related to UMIN activities

The research that continues from the UMIN center is characterized by the following.

■ A focus on health informatics and communication
The Department of Health Communication is the only research institute in Japan that carries out health informatics and communication-related research, addressing areas such as the Internet and satellite communications.

■ Targeting health information science, not health-care information practice

Currently, main topics of the research at most medical informatics programs in Japan focus on information for healthcare practice, such as hospital information systems, electronic medical record systems, tele-medicine, and electronic billing systems. In contrast, the Department of Health Communication has focused on information systems for medical science, such as medical literature databases, data registries for clinical studies, and information systems for medical education.

Most systems developed at the UMIN Center have been subjects for research. In particular, we published and reported systems utilizing advanced technologies and having scientifically meaningful concepts at academic conferences.

■ Information Systems for Clinical Epidemiologic Studies

We have developed and applied information systems for clinical epidemiological studies. Recently, we have

focused on research in electronic formats and standardization that are related to clinical research, such as the Clinical Data Interchange Standards Consortium (CDISC). We utilized the achievements attained by the medical research data center at the UMIN.

■ Research Regarding the Security of an Information Network

The study addresses a Virtual Private Network (VPN), and secure transactions with electronic mail (encryption), which have been also utilized for system management at the UMIN Center.

(2) Research on health communication

Currently, “health communication” is becoming an important concept in the distribution of clinical results for the improvement of population-based clinical outcomes. We have conducted health communication research focusing on knowledge and skills in “informatics” and “communication.” The following are current research topics at the Department of Health Communication.

■ Research on communication to support behavioral change of healthcare consumers

Communication that is easy for patients and citizens to understand and that supports more appropriate decision-making and behavioral change by patients and citizens is the foundation of effective medical care and public health. We are developing and evaluating messages that support behavioral change of healthcare consumers.

■ Research on Media

Mass media and social media have a social influence; however, their quality of information varies. We analyze the health care information distributed by mass media and social media, and examine the impact of media information on health care consumers..

■ Research on Patient-Professional Relationship and Communication

Communication between patients and health care professionals is the foundation of effective health care. We investigate the relationship of patient and provider

characteristics with their communication behaviors, and impacts of the communication on patient outcomes.

■ Research on Health Literacy

The increase in media reports and the rapid expansion of the Internet have rendered various sources of health information more available to the general public. Thus, skills in understanding and applying information about health issues may have a substantial impact on health behaviors and health outcomes. These skills have recently been conceptualized as health literacy. We investigate its relationship with patient and provider communication, and patient health behaviors and outcomes.

References

1. Okuhara T, Kagawa Y, Okada H, Tsunazumi A, Kiuchi T. Intervention studies to encourage HPV vaccination using narrative: A scoping review. *Patient Educ Couns*. 2023 Jun;111:107689.
2. Okada H, Okuhara T, Goto E, Kiuchi T. Association between trust in COVID-19 information sources and engaging in infection prevention behaviors in Japan: A longitudinal study. *Patient Educ Couns*. 2023 Jun;111:107686.
3. Okuhara T, Kagawa Y, Furukawa E, Okada H, Yokota R, Kiuchi T. Realism and length of narrative for further research in health communication. *Patient Educ Couns*. 2023 Sep;114:107859.
4. Furukawa E, Okuhara T, Okada H, Fujitomo Y, Osa M, Hashiba T, Kiuchi T. Evaluating the understandability and actionability of online educational videos on pre-dialysis chronic kidney disease. *Nephrology (Carlton)*. 2023 Nov;28(11):620-628.
5. Furukawa E, Okuhara T, Okada H, Nishiie Y, Kiuchi T. Evaluating the understandability and actionability of online CKD educational materials. *Clin Exp Nephrol*. 2024 Jan;28(1):31-39.
6. Terada M, Okuhara T, Nagasawa T, Okada H, Goto E, Kiuchi T. Public perception of the resumption of HPV vaccine recommendation in Japan: Twitter content analysis. *Health Promot Int*. 2023 Dec 1;38(6):daad153.
7. Okuhara T, Terada M, Kagawa Y, Okada H, Kiuchi T. Anticipated Affect That Encourages or Discourages Human Papillomavirus Vaccination: A Scoping Review. *Vaccines (Basel)*. 2023 Jan 4;11(1):124.
8. Okada H, Okuhara T, Goto E, Kiuchi T. Associations between Vaccination Behavior and Trust in Information Sources Regarding COVID-19 Vaccines under Emergency Approval in Japan: A Cross-Sectional Study. *Vaccines (Basel)*. 2023 Jan 20;11(2):233.
9. Shirabe R, Okada H, Okuhara T, Yokota R, Kiuchi T. Development of the Japanese Version of Pregnancy-Related Anxiety Questionnaire-Revised-2: Measurement and Psychometric Properties. *Healthcare (Basel)*. 2023 Jul 4;11(13):1935.
10. Nagasawa T, Okuhara T, Terada M, Okada H, Goto E, Kiuchi T. Print Materials to Promote Physical Activities in Japan: Content Analysis from a Goal Theory. *Healthcare (Basel)*. 2023 Jan 12;11(2):239.

School of Public Health

2. Behavioral Health Sciences

Departments of Health and Social Behavior & Health Education and Health Sociology

Professor in health and social behavior

Hideki Hashimoto, M.D., D.PH.

Lecturer

Daisuke Takagi, Ph. D. (health and social behavior)

Masamitsu Kamada, Ph. D.(health education and health sociology)

Research Associate

Asuka Kato, MPH, Ph.D. (health and social behavior)

Homepage <http://webpark1166.sakura.ne.jp/>

Introduction and Organization

The department originated as one of the first departments dedicated to health education and behavioral science in Japan, led by former Prof. Emeritus Tadao Miyasaka, who had double degrees of M.D. from the University of Tokyo and MPH in health education from Harvard School of Public Health in 1950s. He was succeeded by a sociologist, former Prof. Kyoichi Sonoda who founded the first health sociology department affiliated with the medical school in Japan. Since then, the program has been leading research focusing on socio-behavioral aspects of health in this country. The legend was extended by former Prof. Chieko Kawada who raised academic and practical attention on the concept of empowerment and adult pedagogy in health education. Since 1997, the department was further evolved by Prof. Ichiro Kai who integrated diverse health and social science disciplines into social gerontology program, and by Associate Prof. Yoshihiko Yamazaki who led sociological research projects on salutogenesis, social stigma, power, and agency in health settings. The

departments were reorganized under the newly established School of Public Health since 2007. In 2012, the Department of Social Gerontology has been renamed as the Department of Health and Social Behavior to apply a life-course perspective to a wider range of social conditions and human well-being.

The new department intends to further integrate health science (medicine and public health) and social science (economics, sociology, and psychology) to reveal a causal mechanism linking social structure and individual health for realizing health equity as a fundamental goal to human security.

Teaching activities

The departments offer five courses in the master degree program for public health, and eight courses in the undergraduate program for the Integrated Health Sciences track.

1. Graduate Courses, School of Public Health

- 1) Health and Society I & II: The course was considerably renewed to focus on inequity,

discrimination, social exclusion, and socio-political activities to overcome these challenges through community building. The renewed course invites adjunctive lecturers specialized in ageism, gender discrimination, child poverty, and foreign residents in Japan, each focusing a specific topic of social determinants of health. Class II offers more practical topics to make changes in social problems through advocacy, social business, and community management, organized in small group work and student presentation of small projects.

- 2) Health Education: The course provides basic knowledge on relevant behavioral theories for health promotion and behavioral modification, followed by case method learning on health educational intervention in community, school, and workplaces. The case discussion was facilitated by invited lecturers to reach practical lessons for effective communication.
 - 3) Health Sociology: Sociology in medicine and sociology applied to health issues are treated in the systemic course of lectures, covering social model of health, medical gaze and socialization of health professionals, phenomenology of chronic illness, and culture and health.
 - 4) Comparative health systems in Asia: Started in 2020, jointly offered by Prof. Soonman Kwon in Seoul National University. The course provides basic frame/theory for comparative analysis of health systems and offers specific country cases for in-class discussion.
2. Undergraduate Courses, School of Integrated Health Sciences
- 1) Introduction to social survey and practice; Provides introductory lecture on sampling, psychometrics, design of social survey and questionnaires. Students are asked to conduct a mini social survey within class on the theme they choose as relevant in their class experience.
 - 2) Health and Society (former Health sociology); Lecture series on social model of health generation, social relationship and health, community network and environment, medicalization, and other relevant health issues.
 - 3) Health education

Case scenario based practicum and lectures on health promotion intervention in clinical, school, and worksite settings.

- 4) Social security and welfare program: Lecture series on the history and the current systems of health care security and welfare policies in this country.
- 5) Integrated Lectures of Public Health Sciences I (jointly offered by the faculty of Health Sciences)
- 6) Scientific writing
- 7) Critical reading/writing of epidemiological studies
- 8) Integrated Practicum of Public Health Sciences II (jointly offered with Department of Medical Ethics).

Research activities

The Department has contributed to empirical and theoretical research on social structure and health/functions. Specifically, the Department has been supporting in the collaboration with the School of Economics of the University of Tokyo and the Research Institute of Economic, Industry, and Technology, The Japanese Study of Ageing and Retirement (J-STAR), a sister study with the U.S. Health and Retirement Study, Study of Health, Ageing, and Retirement in Europe (SHARE), England Longitudinal Survey of Ageing (ELSA), and their global sisters in Asian countries. The scope of JSTAR is diverse; contribution of health for successful ageing, social economic conditions and access to health care, household economy and its impact on life styles such as eating habits and nutrition, impact of retirement onto cognitive function, etc..

Since 2010, the Department has launched another panel study of younger generation, the Japanese study of Stratification, Health, Income, and Neighborhood (J-SHINE) in collaboration with researcher groups on neuroscience, economics, sociology, and social psychology. The aim of this comprehensive panel study is to identify a mechanism how socio-economic environments get to “under-skin” to cause social gradient of health across socio-economic positions. In the year of 2011, the JSHINE conducted a supplemental survey to respondent’s spouse and

children. Main and supplement surveys were followed in 2012 and 2013, respectively. Obtained panel data are made open to a broader range of researchers under the data-control committee, to share analytic scheme and to enhance inter-disciplinary studies so as to better identify common factors as well as unique factors affecting health inequality in Japanese context. Following the third follow-up for children conducted in 2015-2016, and third follow-up of respondent adults in 2017. Facing the COVID-19 pandemic since early 2020, JSHINE project conducted an additional survey in 2020 December to evaluate the social, psychological, and economic impact incurred by the pandemic and related social restriction policies.

Dr. Takagi, in collaboration with Niigata University, is conducting a longitudinal social epidemiological survey of community-dwelling older adults in Myanmar and Malaysia. In these countries that have distinctive stage of economic development, culture, and ageing rate, this study aims at verifying applicability of the existing social models of health and building new theories based on each country's context. A probability proportionate sampling of sites and selection of local investigators have been completed in 2017, and interview surveys is underway in 2020 before COVID-19 and political difficulty started. Dr. Takagi also conducted in collaboration with a municipal government in Chiba Prefecture a survey targeting regional crime prevalence and the preventive effect through social network structure by using sociometric measurement of social network in a community.

Dr. Kamada, in collaboration with Tokyo Medical University, Harvard University, and Utsunomiya Municipality authority has been conducting a community-based intervention program to enhance exercise habits. He is also actively engaged in developing a gamification program through smartphone to enhance walking habits among the community, of which results are to be published. Dr. Kamada most recently works to develop an application software to objectively obtain daily step counts of iPhone users that would make a technical innovation to facilitate social epidemiology of physical activities in fields.

Dr. Kato, in collaboration with the Department of Diabetes and Metabolic Diseases in the University of

Tokyo Hospital, and other leading clinical institutes, has been conducting the development of self-learning materials to help people having diabetes counter against self-stigma. She is recently invited as a member of an international specialist panel to prepare for an international consensus statement to stop stigma against people having diabetes, expectedly published in *Lancet Diabetes and Endocrinology* in early 2024.

Other Social activities

Each of the faculty members has contributed as an academic advisor for health promotion policy program in several local governments. Dr. Kato serves as an academic advocator for people having diabetes.

Publications

1. Peer reviewed journals
2. 大川卓朗・高木大資. COVID-19 流行前後の健康関連行動の変化と時間割引率の関連：J-SHINE2017、2020 を用いた分析. 厚生指標. 70(3), 26-34, 2023.
3. Yano M, Ichikawa M, Hirai H, Ikai T, Kondo N, Takagi D. Neighbourhood transportation, elapsed years, and well-being after surrendering the driver's licence in older Japanese adults: The JAGES longitudinal study. *Arch Gerontol Geriatr.* 2023 Apr;107:104898.doi: 10.1016/j.archger.2022.104898.
4. Murakami K, Kuriyama S, Hashimoto H. Economic, cognitive, and social paths of education to health-related behaviors: evidence from a population-based study in Japan. *Environ Health Prev Med.* 2023;28:9. doi: 10.1265/ehpm.22-00178.
5. Kim H, Yoon NH, Hahn Y, Hashimoto H. "Explaining Variations in Long-term Care Use and Expenditures Under the Public Long-term Care Insurance Systems: A Case Study Comparison of Korea and Japan". *International Journal of Health Policy and Management*, 2023, 12;1-11.doi: 10.34172/ijhpm.2022.6640.
6. Murakami K, Kuriyama S, Hashimoto H. General health literacy, COVID-19-related health literacy, and protective behaviors: evidence from a

- population-based study in Japan. *Front Public Health*. 2023 Sep 18;11:1208815. doi: 10.3389/fpubh.2023.1208815.
7. Arakawa Y, Haseda M, Inoue K, Nishioka D, Kino S, Nishi D, Hashimoto H, Kondo N. Effectiveness of mHealth consultation services for preventing postpartum depressive symptoms: a randomized clinical trial. *BMC Med*. 2023 Jun 26;21(1):221. doi: 10.1186/s12916-023-02918-3.
 8. Murakami K, Aida J, Kuriyama S, Hashimoto H. Associations of health literacy with dental care use and oral health status in Japan. *BMC Public Health*. 2023 Jun 5;23(1):1074. doi: 10.1186/s12889-023-15866-7.
 9. Fujii K, Hashimoto H. Socio-psychological factors associated with anticipated stigma toward COVID-19: a cross-sectional study in Japan. *BMC Public Health*. 2023 Jun 27;23(1):1245. doi: 10.1186/s12889-023-16159-9.
 10. Lai ETC, Chiang TL, Kim CY, Hashimoto H, Marmot M, Woo J. The determinants of longevity: The perspectives from East Asian economies. *J Am Geriatr Soc*. 2023 Oct;71(10):3338-3341. doi: 10.1111/jgs.18418.
 11. Matsuoka Y, Haseda M, Kanamori M, Sato K, Amemiya A, Ojima T, Takagi D, Hanazato M, Kondo N. Does disaster-related relocation impact mental health via changes in group participation among older adults? causal mediation analysis of a pre-post disaster study of the 2016 Kumamoto earthquake. *BMC Public Health*. 2023 Oct 11;23:1982. doi: 10.1186/s12889-023-16877-0.
 12. Nagamine Y, Shobugawa Y, Sasaki Y, Takagi D, Fujiwara T, Khin Y P, Nozaki I, Shirakura Y, Thi L K, Ei Z P, Thae Z, Win H H. Associations between socioeconomic status and adherence to hypertension treatment among older adults in urban and rural areas in Myanmar: a cross-sectional study using baseline data from the JAGES in Myanmar prospective cohort study. *BMJ Open*. 2023 Jan 17; 13: e065370. doi: 10.1136/bmjopen-2022-065370. doi: 10.1136/bmjopen-2022-065370.
 13. Abe T, Okuyama K, Kamada M, Kitayuguchi J, Hamano T, Waki H, Nabika T, Isomura M, Sundquist K. Association between flexibility activity and blood-pressure change among older adults in Japan: A 5-year longitudinal study. *Scand J Med Sci Sports*. 2023; 00: 1-8. <https://doi.org/10.1111/sms.14386>.
 14. Murphy J, Milton K, McLaughlin M, Shilton T, McLoughlin G, Reece LJ, Mair JL, Direito A, Kariippanon KE, Mackenzie KJ, Mavilidi MF, Shellington EM, Kamada M, Heron L, Jauregui E, Abdeta C, Pina I, Pinto R, Sutherland R. Advocating for implementation of the Global Action Plan on Physical Activity: challenges and support requirements. *J Phys Act Health*. 20(1): 10-19, 2023. <https://doi.org/10.1123/jpah.2022-0357>.
 15. Abe T, Kitayuguchi J, Fukushima N, Kamada M, Okada S, Tanaka C, Inoue S, Mutoh Y. Assessing the implementation of an early childhood exercise program for preschool workers using the PAIREM model. *Res Exerc Epidemiol*. 25(2): 152-162, 2023. doi: 10.24804/ree.2304 (Japanese)

School of Public Health

3. Health Services Sciences

Department of Clinical Information Engineering

Professor

Hiroshi Oyama, M.D., Ph.D.

Assistant professor

Kelssy Hitomi dos Santos Kawata, Ph.D.

※The following information is the same as that of the previous year for certain reasons.

Homepage: https://webpark1893.sakura.ne.jp/wp/home/cie_en/

Introduction and Organization

Information engineering significantly impacts computer hardware, software, and data processing. It is a discipline that seeks objective data and emphasizes the conception of new data transfer methods, storage, processing, and input/output. It also targets research on developing computer devices and systems.

Reviewing the history of the application of computers in medicine, calculating machines for supporting scientists and technologists first appeared in the 1950s. In the 1960s, computers were used for accounting and various statistics. The personal computer appeared in the 1980s and was adopted for personal use in many professions. The systematization of large hospitals, such as university hospitals, pushed ahead rapidly.

In the 1990s, the computer began to help human thinking, such as in presentations, design, and discovery. When computers became connected through the internet, the distribution of information became very easy and rapid, both within organizations and internationally.

In 2003, a high-quality, "finished" sequence of the human genome was completed. At the dawn of the twenty-first century, bioinformatics appeared as a new discipline, one that uses applied mathematics, informatics, statistics, computer science, and biochemistry to solve biological problems. In medicine,

advanced information technologies have been applied to health information infrastructures, electrical clinical guidelines, and knowledge navigation systems.

In response to the needs of the time, the Department of Clinical Information Engineering (CIE) was established at the School of Public Health in April 2007. Its predecessor was the clinical information engineering division of clinical bioinformatics, using Special Coordination Funds for Promoting Science and Technology from Japan's Ministry of Education, Culture, Sports, Science, and Technology.

Teaching activities

The Department of Clinical Information Engineering aims to nurture talented people with special knowledge and skills at an international level to apply advanced information technologies to practical projects in clinical medicine and the health sciences. It offers courses on information system design, development methodology, evaluation, and project management in biomedicine, health care, and public health in the School of Public Health, and data mining and virtual reality for clinical decision-making in social medicine.

Famous visiting lecturers and researchers from the National Cancer Center and other universities have given lectures here, furthering our hope of becoming a world leader in this field.

The education of graduate students is based on

weekly conferences at which the students present their research projects' progress and discuss their future directions.

Research activities

Our research covers biomedical computer applications focusing on data (collection, analysis, and representation). It constitutes a combination of information science, computer science, and clinical science designed to assist in managing and processing data, information, and knowledge to support the practice and delivery of clinical care. Our laboratory is engaged in the following research activities:

A) Computer Graphics & Virtual Reality (VR) for Medical Science: Our research has three goals: to improve the living conditions of in-patients with limited physical activity by providing virtual experiences, to develop new diagnostic methods using medical imaging, and to develop a surgical edutainment and preoperative surgical planning support system in virtual space.

The advantages of simulating surgical procedures using VR techniques include (1) practicing the surgical procedure and image-based training; (2) planning the surgical procedure for individual patients preoperatively using VR images modeled from the patient's preoperative computed tomography (CT) or magnetic resonance (MR) images, in collaboration with the Department of Neurosurgery; (3) allowing supervisors to evaluate a procedure objectively; and (4) helping patients and their families to better understand the surgical procedure before and after the operation.

B) Social Information Engineering for Public Health (Public Health Informatics): Our laboratory researches new tools and methodologies for applying information, computer science, and technology to public health practice, research, and learning. We are studying differences in the computerization of public health in the US and Japan.

References

1. Lem, W. G., dos Santos Kawata, K. H., Kobayashi, T., & Oyama, H. (2023). Public Stigma Related to People With Mental Health Conditions Among Japanese Company Employees. *Journal of Clinical Medicine Research*, 15(3), 139-147.
2. Koike, T., Tanaka, S., Kin, T., Suzuki, Y., Takayanagi, S., Takami, H., ... Oyama, H. & Saito, N. (2022). Accurate Preoperative Identification of Motor Speech Area as Termination of Arcuate Fasciculus Depicted by Q-Ball Imaging Tractography. *World Neurosurgery*, 164, e764-e7
3. Nagayo, Y., Saito, T., & Oyama, H. (2022). Augmented reality self-training system for suturing in open surgery: A randomized controlled trial. *International Journal of Surgery*, 106650.

Department of Global Environmental Health

Associate Professor

Yoonhee Kim, Ph.D.

Homepage <https://sites.google.com/m.u-tokyo.ac.jp/envhealth/>

Introduction and Organization

The Department of Global Environmental Health (GEH) started under the School of Public Health (SPH), Graduate School of Medicine, in April 2018 and has contributed to the master's program (MPH). It has been affiliated with the School of International Health (SIH), Graduate School of Medicine since July 2018 as an Associate Department, accepting master's and doctoral students.

The GEH aims:

1. To study relationships between environmental exposure and human health
2. To produce well-educated professionals with the academic knowledge and ability to undertake environmental epidemiological research

Education

This department provides two postgraduate courses at SPH: 1) Environmental Health and 2) Methods for Environmental Health Research. The former is an introductory course in environmental epidemiology that introduces basic concepts and methods to assess a potential relationship between environmental stressors and health outcomes at both individual and population levels. It provides state-of-the-art scientific knowledge and interpretation for health risk/impact assessment in environmental health perspectives. The latter is an advanced course dealing with statistical and epidemiological methodologies in environmental epidemiology that provides the theory and practice of a specific method to estimate the short-term effects of

environmental risk factors on human health.

Journal Club

GEH has participated in a biweekly conference call with multiple schools/institutes* to read and discuss articles in environmental epidemiology.

*The University of Tokyo (Japan), University of Tsukuba (Japan), Hokkaido University (Japan), Nagasaki University (Japan), National Institute for Environmental Studies (Japan), Seoul National University (South Korea), Pusan National University (South Korea), Korea Advanced Institute of Science & Technology (KAIST) (South Korea)

GEH Seminar

Every other Tuesday, 11:00-12:30

All GEH members, including graduate students, share fundamental knowledge and practices they have learned from textbooks and research articles in environmental epidemiology, such as R programming and its applications for time-series regression analysis and spatial analysis. The GEH members also share their ongoing research projects and engage in open discussions on their progress.

All course lectures, thesis advising, and discussions in seminars are carried out in English.

Research

Our research interests particularly focus on climate change and air pollution in human populations in the field of environmental epidemiology. We address the scientific questions of how they link, quantify the health risks of a specific environmental factor, and further investigate social determinants that could

potentially modify the exposure-response relationships.

Our research collaborations include:

1. Global perspectives of seasonal variability of suicide and the short-term associations between suicide and ambient temperature and air pollution using a large-scale daily time-series database across 26 countries, as a part of the Multi-Country Multi-City (MCC) Collaborative Research Network
2. Health risk assessment of climate change and air pollution in Asian countries, including Japan, South Korea, China, Lao PDR, and Thailand.
3. Nationwide studies on the short-term associations between suicide and ambient temperature and air pollution in Finland
4. Establishment of an early warning system for malaria incidence in southern Africa
5. Baseline assessment of climate change impacts on human health in Kiribati: a Pacific island country.

Publications

1. Pillay MT, Minakawa N, Kim Y, Kgalane N, Ratnam JV, Behera SK, Hashizume M, Sweijd N. Utilizing a novel high-resolution malaria dataset for climate-informed predictions with a deep learning transformer model. *Scientific Reports* 2023;13:23091.
2. Sugeno M, Kawazu EC, Kim Hyun, Banouvong V, Pehlivan N, Gilfillan D, Kim Ho, Kim Y. Association between environmental factors and dengue incidence in the Lao People's Democratic Republic: a nationwide time-series study. *BMC Public Health* 2023;23:2348.
3. Thawonmas R, Hashizume M, Kim Y. Projections of temperature-related suicide under climate change scenarios in Japan. *Environmental Health Perspectives* 2023;131(11):117012.
4. Kim Y, Oka K, Kawazu EC, Ng CFS, Seposo X, Ueda K, Hashizume M, Honda Y. Enhancing Health Resilience in Japan in a Changing Climate. *The Lancet Regional Health - Western Pacific* 2023:100970.
5. Chua PLC, Takane Y, Ng CFS, Oka K, Honda Y, Kim Y, Hashizume M. Net impact of air conditioning on heat-related mortality in Japanese cities. *Environment International* 2023;181:108310.
6. Yang Z, Huang W, McKenzie JE, Xu R, Yu P, Ye T, on behalf of MCC Collaborative Research Network. Mortality risks associated with floods in 761 communities worldwide: time series study. *BMJ* 2023;383:e075081.
7. Okada A, Yamana H, Pan R, Yamaguchi S, Kumazawa R, Matsui H, Fushimi K, Honda Y, Nangaku M, Yamauchi T, Yasunaga H, Kadowaki T, Kim Y. Effect modification of the association between temperature variability and hospitalization for cardiovascular disease by comorbid diabetes mellitus: a nationwide time-stratified case-crossover analysis. *Diabetes Research and Clinical Practice* 2023;202:110771.
8. Kim SE, Kim Y, Hashizume M, Honda Y, Kazutaka O, Hijioka Y, Kim H. Positive Association of Aggression with Ambient Temperature. *Yale Journal of Biology and Medicine* 2023;96(2):189-196.
9. He Q, Liu L, Zhang H, Chen R, Dong G, Yan LL, Zeng Y, Kim Y, Ji JS. Environmental Greenspace, Subjective Well-Being, and All-Cause Mortality in Elderly Chinese: Association and Mediation Study in a Prospective Cohort. *Environmental Research* 2023;227:115732.
10. Pan R, Okada A, Yamana H, Yasunaga H, Kumazawa R, Matsui H, Fushimi K, Honda Y, Kim Y. Association between ambient temperature and cause-specific cardiovascular disease admissions in Japan: A nationwide study. *Environmental Research* 2023;225:115610.
11. Lin SY, Ng CFS, Kim Y, Htay ZW, Cao AQ, Pan R, Hashizume M. Ambient Temperature and Nervous System Diseases-related Mortality in Japan from 2010 to 2019: A Time-Stratified Case-Crossover Analysis. *Science of The Total Environment* 2023;867:161464.
12. Nishikawa H, Seposo XT, Madaniyazi L, Kim Y, Tobias A, Yamagami M, Kim SE, Takami A, Sugata S, Honda Y, Ueda K, Hashizume M, Ng CFS. Long-term trends in mortality risk associated with short-term exposure to air pollution in 10 Japanese cities between 1977 and

2015. *Environmental Research* 2023:219:115108.
13. Phung VLH, Oka K, Honda Y, Hijioka Y, Ueda K, Seposo XT, Sahani M, Mahiyuddin WRW, Kim Y. Daily temperature effects on under-five mortality in a tropical climate country and the role of local characteristics. *Environmental Research* 2023:218:114988.

Endowed Department

Department of Artificial Intelligence in Healthcare

Project Professor

Kengo Miyo, Ph.D.

Project Associate Professor

Yoshimasa Kawazoe, M.D., Ph.D.

Project Research Associate

Emiko Shinohara, Ph.D.

Project Researcher

Kiminori Shimamoto, M.E.

Homepage <https://ai-health.m.u-tokyo.ac.jp/>

Introduction and Organization

Practical applications based on the development of AI technology call for a fundamental transformation of the industrial structure. The global spread of COVID-19 has significantly changed the way medical care, economy, and society operate. To maintain and further develop the quality of the Japanese society, which some consider to be in decline because of the falling birth rate, rational and efficient social management based on information and communications technology (ICT) as well as artificial intelligence (AI), become indispensable. This course was established in 2018 at the University of Tokyo Hospital Department of Planning, Information and Management (Graduate School of Medicine Department of Biomedical Informatics) as a collaborative course. Since August 2023, it has been operating as the Department of Medical AI and Digital Twin Development, focusing on demonstrating new forms of medical services and advancing the development of foundational technologies. The course aims to contribute to human resource development by creating a support hub for researchers in this field. Additionally, it strives to contribute to the advancement of healthcare by fostering collaborative

research that transcends the boundaries of faculties and universities.

Teaching activities

We have promoted activities to train researchers as well as students in this area inside and outside the university. In 2022, we were in charge of the medical informatics course at the University of Tokyo Faculty of Medicine designed for 4th-year students. We have also taught courses to Graduate School of Medicine School of Public Health professional master's degree students and have contributed to courses on medical RWD human resources development projects for working adults. The courses have focused on AI-related technologies in medical informatics. We have provided research guidance to doctoral students of the Graduate School of Medicine Department of Biomedical Informatics as well as Reproductive, Developmental and Aging Sciences; research guidance was provided at the individual level.

Research activities

Development of Medical Digital Twins

The 3rd Phase of the Strategic Innovation Promotion

Program (SIP) "Development of an Integrated Healthcare System," led by Program Director Dr. Ryozi Nagai, President of Jichi Medical University, aims to autonomously promote the cycle of "knowledge discovery" and "healthcare delivery" in the medical field through the implementation of medical digital twins. This program focuses on developing standardized platforms for electronic health records and personal health records, creating life record digital twins for chronological collection of individual health data, and constructing an integrated healthcare system to enhance medical quality, support patients and physicians, and evaluate medical products and devices. Our department actively contributes to this initiative through two key subthemes: Subtheme B5, led by Professor Kengo Miyo, which focuses on developing a traceability system for medical devices to support their improvement and optimize resource allocation and hospital management; and Subtheme D1, led by Associate Professor Yoshimasa Kawazoe, which aims to create a cross-organizational medical data infrastructure transcending the boundaries of medical institutions, vendors, and systems. Through these efforts, our department is at the forefront of medical digital twin development, working towards revolutionizing healthcare delivery and management.

Development of natural language processing technique for medical treatment

Symptoms and clinical findings, the relationship between these and treatment actions are freely described in the medical records of patients, unlike the test values. The structuring and analysis of such textual information are expected to contribute to new clinical medical discoveries and medical safety. The development of a natural language processing technique for structuring text information requires an annotated text corpus with an annotated target text and specific information on the subject of interest (symptoms, findings, etc.). In this course, we plan to target case reports of intractable diseases designated by the Ministry of Health, Labor and Welfare with the aim of developing a case report corpus that consistently and comprehensively annotates expressions that indicate the clinical condition of patients and the treatments that have been performed. By using the annotated information, we aim to extract

information, such as the name of the patient's disease, the presence (or absence) of the kind of symptoms, the location of the symptoms, whether they are mild or severe, whether they are related to the treatment performed, the outcome at discharge, etc., from the text for subsequent analysis. We are also developing a machine learning model that accurately reproduces the annotated information. The natural language processing technique we are planning on developing will be able to create text for the clinical fields of medical records, structuring the details of the data.

Application of natural language processing technology

By analyzing electronic medical chart records using computers, we anticipate uncovering new insights into medicine and healthcare. These charts capture a variety of data, of which the freely written text holds significant information. Nevertheless, this textual data has historically posed technical challenges for computerized analysis. Supported by the Japan Science and Technology Agency (JST), this course highlights our use of natural language processing technology, co-developed with our research partners. Our goal is to further research into unveiling new therapeutic effects from diverse electronic medical chart data. Our studies have already demonstrated the ability to accurately identify known adverse events from chemotherapy within these texts. Moving forward, our research endeavors will focus on discovering novel therapeutic benefits of combined drug treatments, striving to enhance the safety of patient care.

Social activities

1. Gave lectures at various seminars, describing ICT related issues in the medical field utilizing AI.
2. Participated in the HL7-FHIR (Fast Healthcare Interoperability Resources) implementation study working group established under the Japan Association of Medical Informatics Research Group "Academic Research Group for Next Generation Healthcare Record System," and studied the details necessary for proceeding with the implementation of HL7-FHIR in Japan.
3. Involved in the discussions of the collection of clinical information and the construction of

information systems as a member of the Designated Core Hospitals for Cancer Genomic Medicine Working Group (RPWG).

4. Promoted the standardization of disease names registered in electronic medical records under the standard disease name master working group.

References

1. Yoneda K, Seki T, Kawazoe Y, Ohe K, Takahashi N; Neonatal Research Network of Japan. Immediate postnatal prediction of death or bronchopulmonary dysplasia among very preterm and very low birth weight infants based on gradient boosting decision trees algorithm: A nationwide database study in Japan. *PLoS One*. 2024 Mar 27;19(3):e0300817. doi: 10.1371/journal.pone.0300817.
2. Seki T, Kawazoe Y, Ohe K. Clinical Feature Vector Generation using Unsupervised Graph Representation Learning from Heterogeneous Medical Records. *AMIA Annu Symp Proc*. 2024 Jan 11;2023:618-623. PMID: 38222342; PMCID: PMC10785854.
3. Shibata D, Shinohara E, Shimamoto K, Kawazoe Y. Towards Structuring Clinical Texts: Joint Entity and Relation Extraction from Japanese Case Report Corpus. *Stud Health Technol Inform*. 2024 Jan 25;310:559-563. doi: 10.3233/SHTI 231027. PMID: 38269871.
4. Seki T, Kawazoe Y, Ohe K. Graph Representation Learning-Based Fixed-Length Clinical Feature Vector Generation from Heterogeneous Medical Records. *Stud Health Technol Inform*. 2024 Jan 25;310:715-719. doi: 10.3233/SHTI 231058. PMID: 38269902.
5. Hirabayashi M, Shibata D, Shinohara E, Kawazoe Y. Influence of Tweets Indicating False Rumors on COVID-19 Vaccination: Case Study. *JMIR Form Res*. 2023 Sep 5;7:e45867. doi: 10.2196/45867.

Department of Osteoimmunology

Project Associate Professor

Kazuo Okamoto, Ph.D.

Project Assistant Professor

Masayuki Tsukasaki, Ph.D.

※The following information is the same as that of the previous year for certain reasons.

Homepage <http://www.osteoimmunology.com/kifu/index.html>

Introduction and Organization

Bone is a key component of the skeletal-locomotor system and serves as a calcium reservoir regulated by the endocrine system in vertebrates. Bone also acts as the “primary lymphoid organ” that harbors and mobilizes hematopoietic stem cells (HSCs) and immune progenitor cells. Furthermore, the bone and immune systems are closely related through a number of shared regulatory molecules including cytokines, receptors and signaling molecules. Osteoimmunology is an interdisciplinary research field that investigates the shared mechanisms and crosstalks between the bone and the immune systems. Studies on bone destruction associated rheumatoid arthritis (RA) have highlighted regulation of bone by the immune cells and promoted this field. As seen in the clinical benefits of anti-TNF antibody, anti-IL-6 antibody and CTLA4-Ig on inflammation and osteoclast differentiation for the treatment of RA, the osteoimmunological insight is now of growing importance in clinical applications. It is necessary to comprehensively understand the interplay between bone and immune systems for elucidation of the molecular mechanisms underlying the pathogenesis of various bone diseases (osteoporosis, osteoarthritis, periodontal disease etc.) and immune diseases (autoimmune diseases, infectious diseases etc.).

Osteoimmunology is now emphasized by not only the academic but also clinical sides, and the international competition has intensified in both basic

and pharmaceutical researches. This department was founded as a new department focusing on the osteoimmunology in May 2016. The second term started in May 2019, and was temporarily suspended in June 2022. Subsequently, the third phase started in November 2022, with support from AYUMI Pharmaceutical Corporation, ELECOM, JCR Pharmaceuticals, Kondo Cotton Spinning, MIKIHOUSE, MITSUI FUDOSAN, Meiji, Noevir, TAKENAKA, TENNENBUTSU IKAGAKU KENKYU ZAIDAN and Yakult. We aim to understand the mechanisms underlying the pathogenesis of various skeletal and immune diseases, and to provide the molecular basis for novel drug discovery in the field.

Teaching activities

As for under-graduate education, our department takes a part in systemic lectures. We train post-doctoral fellows, graduate and post-graduate students in Department of Immunology, Graduate School of Medicine and Faculty of Medicine, The University of Tokyo.

Research activities

By extending the concept of osteoimmunology to various skeletal and immune diseases, we aim to comprehensively elucidate the crosstalks between the bone and immune systems involved in the pathogenesis of the diseases, and provide the molecular

basis for novel therapeutic strategies. Our achievement would help to improve the welfare and raise the level of medical treatment in the world.

Main research achievements

RANKL in bone, immunity and cancer

Bone is a dynamic organ that continuously undergoes a process involving resorption and formation (bone remodeling), which are mediated by osteoclasts and osteoblasts, respectively. An imbalance of bone resorption and formation is often central to metabolic bone diseases, including bone destruction in RA, postmenopausal osteoporosis, bone tumors and osteopetrosis. Osteoclasts are large, multinucleated cells formed by the fusion of precursor cells of monocyte/macrophage lineage. Mature osteoclasts degrade bone matrix proteins by secreting proteolytic enzymes and decalcify the inorganic components of bone by releasing hydrochloric acid. RANKL is an essential cytokine for osteoclast differentiation. RANKL, which are produced by the supporting mesenchymal cells including osteoblasts, osteocytes and synovial fibroblasts, binds to its receptor RANK expressed on osteoclast precursor cells. Mice with a disruption of either *Rank* or *Rankl* exhibit severe osteopetrosis accompanied by a tooth eruption defect resulting from a complete lack of osteoclasts. Mutations in the *RANK* and *RANKL* genes have been identified in human patients with bone disorders such as autosomal recessive osteopetrosis. These genetic findings clearly demonstrate that RANK/RANKL signaling is essential for osteoclastogenesis *in vivo*. We aim to elucidate the molecular mechanism underlying RANKL-induced osteoclast differentiation, in order to develop the novel therapeutic strategies for the treatment of various bone diseases such as RA and osteoporosis (Tsukasaki et al, *J Bone Miner Res*, 2016; Okamoto et al, *Physiol Rev*, 2017). Recently, we have elucidated the mechanism of osteoclastogenesis at the single cell level by single-cell RNA sequencing analysis. Osteoclast differentiation pathway can be divided into multi stages, and we identified a number of genes that determine each differentiation stage. We found that the transcriptional regulator *Cited2* regulates the terminal differentiation step by promoting cell cycle arrest. The single-cell analysis data covering all

pathways of osteoclast differentiation would be a useful resource for the development of therapeutic treatments targeting osteoclasts (Tsukasaki et al, *Nat Metab*, 2020).

RANKL plays crucial roles in not only osteoclast differentiation but also the immune system, including lymph node development, thymic epithelial cell differentiation and M cell differentiation in gut. Thus, RANKL is one of the most important factors explicitly linking the skeletal and immune systems. RANKL is synthesized as a membrane-bound molecule, which is cleaved into the soluble form by proteases. Both forms function as agonistic ligands for RANK. However, the functional difference between the membrane-bound and soluble forms of RANKL had been poorly understood *in vivo*. Thus, we tried to elucidate the physiological and pathological significances of soluble RANKL by generating mice that selectively lack soluble RANKL. Soluble RANKL-deficient mice did not show any discernible osteopetrotic phenotype. In addition, soluble RANKL made no contribution to ovariectomy-induced osteoporosis. Thus, membrane-bound RANKL mainly functions in osteoclast differentiation *in vivo*. Furthermore, unlike RANKL-null mice, soluble RANKL-deficient mice had normal development of the immune organs, including lymph node development, thymic medullary epithelial cell differentiation and M cell differentiation. Collectively, we demonstrated that soluble RANKL is dispensable for physiological regulation of bone and immune systems (Asano et al, *Nat Metab*, 2019).

RANKL also deeply contributes to the pathogenesis of bone metastasis. In bone, tumor cells induce the RANKL expression in osteoblasts through the production of PTHrP and IL-6. RANKL promotes osteoclastic bone resorption, which provides space for tumor expansion and releases certain growth factors from the degraded bone matrices to stimulate tumor growth, forming a vicious cycle. In addition, RANK is expressed at high levels on many different epithelial tumor cells that preferentially metastasize to bone. RANKL acts directly on RANK-expressing tumor cells to increase tumor migration to bone. Notably, soluble RANKL contributes to bone metastasis by exerting a chemotactic activity in tumor cells expressing RANK. Soluble RANKL deficiency in

mice markedly suppressed the metastasis of murine melanoma cell line B16F10 and breast cancer cell line EO771, both of which express RANK, to bone (Asano et al, *Nat Metab*, 2019; Okamoto, *J Bone Miner Metab*, 2021). Interestingly, the recent human study indicates that breast cancer patients with high levels of serum RANKL had an increased risk of developing bone metastases. Thus, to measure the serum RANKL level may help identify the patients who have a high risk of development of bone metastasis.

In rheumatoid arthritis, synovial fibroblasts act as the main source of RANKL that induces osteoclastic bone resorption in joints. Recent single cell analyses have shown that synovial fibroblasts could be classified into two subsets, inflammation type and tissue-destructive type. By analyzing the mechanism of transcriptional regulation of RANKL, we revealed that transcriptional factor ETS1 drives the polarization toward tissue-destructive fibroblasts in rheumatoid arthritis (Yan et al, *Nat Immunol*, 2022).

The RANKL decoy receptor osteoprotegerin (OPG) regulates bone metabolism and the immune organ development as an inhibitor of RANKL signal. OPG is a soluble protein, which also circulates in the blood. By analyzing osteoblast-specific, thymic epithelial cell-specific and intestinal epithelial cell-specific OPG-deficient mice, we showed that bone metabolism, thymic epithelial cell differentiation and M cell differentiation is controlled by OPG locally produced in bone, thymus and intestine, respectively, but not by circulating OPG. The findings further revealed the importance of local regulation of the RANKL/RANK system (Tsukasaki et al, *Cell Rep*, 2020).

Recently, a fully human anti-RANKL neutralizing antibody has been introduced for the treatment of osteoporosis and skeletal-related events by bone tumors. We have evaluated the efficacy of the novel small molecule inhibitor against RANKL signaling using mouse disease models (Guerrini et al, *Immunity*, 2015). Using the mouse models of bone metastasis, we have demonstrated that oral administration of the small-molecule RANKL inhibitor against RANKL suppressed the metastasis of human breast cancer cell line and murine melanoma cell line to bone (Nakai et al, *Bone Res*, 2019).

Roles of T cells in bone destruction associated with inflammation

The bone destruction in RA is the result of the enhanced osteoclast activity due to the inflammatory responses triggered by the activation of pathogenic helper T cells. We previously reported using a mouse model of autoimmune arthritis that a subset of Foxp3⁺ T cells loses Foxp3 expression under arthritic conditions and converts into IL-17-producing T cells (called exFoxp3Th17 cells). exFoxp3Th17 cells display a greater capacity for inducing both synovitis and osteoclastic bone resorption (Komatsu et al, *Nat Med*, 2014). The conversion of Foxp3⁺ T cells into effector T cells has also been observed in various diseases such as diabetes and multiple sclerosis. We have recently demonstrated that exFoxp3Th17 cells also act as osteoclastogenic T cells in alveolar bone destruction in periodontitis. exFoxp3Th17 cells accumulate in periodontitis tissues in response to oral bacteria, and stimulate mesenchymal cells including osteoblastic cells and periodontal ligament cells to induce RANKL. We found that exFoxp3Th17 cells protect against bacteria by evoking mucosal immune responses as well as removing the tooth (Tsukasaki et al, *Nat Commun*, 2018). Our findings introduce a new concept that bone destruction contributes to the host defense against oral bacteria in periodontitis.

In recent years, Jak inhibitors have attracted attention as potential agents for the autoimmune diseases such as rheumatoid arthritis. We have recently found that protein arginine methylation, a post-translational modification, is critically involved in the regulation of the Jak signaling pathway. T cell-specific deficiency of the arginine methyltransferase PRMT5 led to a decrease in the number of peripheral CD4, CD8 and regulatory T cells, and an almost complete loss of iNKT cells. PRMT5-mediated arginine methylation was essential for the expression of the cytokine-signal-transducing components, the common cytokine receptor γ -chain (γ c) and JAK3, which are required for the development of iNKT cells and the proliferation and survival of peripheral T cells. PRMT5 induced the arginine methylation of the spliceosomal component SmD3 that promoted the splicing of pre-mRNA encoding γ c and JAK3 (Inoue et al, *Nature Immunol*, 2018). This study presented a novel regulatory mechanism

governing γc family cytokine-Jak3 signaling in T cells.

Immune regulation by osteoblast in the bone marrow

HSCs have the capacity to differentiate into all immune cells, and their activities require extrinsic signals from the microenvironments (niches) in the bone marrow. Various cell types including CXCL12-abundant reticular (CAR) cells, leptin receptor-expressing perivascular stromal cells, Nestin⁺ perivascular cells and neural cells have been shown to be important for HSC maintenance. Although osteoblasts were first reported to function as the HSC niche in the early 2000s, the significance of the osteoblastic niche had remained unclear. In order to clarify the role of osteoblasts in the hematopoiesis in the bone marrow, we generated an inducible deletion system of osteoblasts in adult mice. We found that inducible ablation of osteoblast had no effect on the HSCs but reduced the number of both common lymphoid progenitors in the bone marrow and lymphocytes in the periphery. Osteoblast-derived IL-7 is required for development of common lymphoid progenitors in the bone marrow (Terashima et al, *Immunity*, 2016). Moreover, we showed that sepsis reduces the osteoblast number, which induces lymphopenia through IL-7 downregulation. Our study identified a novel mechanism by which bone cells regulate the immune system.

Huynh NC, Muro R, Ando Y, Seki Y, Terashima A, Pluemsakunthai W, Nitta T, Nakamura T, Nakashima T, Ohba S, Akiyama H, Okamoto K, Baron R, Takayanagi H. Periosteal stem cells control growth plate stem cells during postnatal skeletal growth. *Nat Commun.* 13: 4166, 2022

4. Tsukasaki M, Takayanagi H. Osteoclast biology in the single-cell era. *Inflamm Regen.* 42: 27, 2022

References

1. Yan M, Komatsu N, Muro R, Huynh NC, Tomofuji Y, Okada Y, Suzuki HI, Takaba H, Kitazawa R, Kitazawa S, Pluemsakunthai W, Mitsui Y, Satoh T, Okamura T, Nitta T, Im SH, Kim CJ, Kollias G, Tanaka S, Okamoto K, Tsukasaki M, Takayanagi H. ETS1 governs pathological tissue-remodeling programs in disease-associated fibroblasts. *Nat Immunol.* 23:1330-1341, 2022
2. Ono T, Denda R, Tsukahara Y, Nakamura T, Okamoto K, Takayanagi H, Nakashima T. Simultaneous augmentation of muscle and bone by locomimeticism through calcium-PGC-1 β signaling. *Bone Res.* 10:52, 2022
3. Tsukasaki M, Komatsu N, Negishi-Koga T,

Department of Computational Diagnostic Radiology and Preventive Medicine

Project Professor

Naoto Hayashi, M.D.,Ph.D.

Project Associate Professor

Takeharu Yoshikawa, M.D.,Ph.D.

Project Research Associate

Kensuke Asaba, M.D.,Ph.D., Katsuhiko Koyama, M.D., Ph.D., Takayuki Fujiwara, M.D., Ph.D., Takahiro Nakao, M.D., Ph.D., Kanna Fujita, M.D., Ph.D., Mai Shimbo, M.D., Ph.D.
Saori Koshino, M.D., Ph.D.

Project researcher

Masaya Akiyama, M.S., Alam Md Ashraful, Ph.D., Yukihiro Nomura, Ph.D., R.T.

※The following information is the same as that of the previous year for certain reasons.

Homepage <http://www.ut-radiology.umin.jp/division/cdrpm.html>

Introduction and Organization

The Department of Computational Diagnostic Radiology and Preventive Medicine (CDRPM) was established in May 2005. It is under the supervision of the Department of Radiology.

The aim of our research project is as follows: (1) to create a large database of health screening clinical data including medical images, (2) to develop methods to analyze large volumes of medical images and to search for algorithms to detect subtle abnormal findings in these images, and (3) to evaluate the clinical usefulness of such image processing methods and to apply the system in clinical settings.

The department comprises twelve professors and three project researchers, along with a medical staff of approximately 70 employees in the health-screening center.

Clinical Activities

CDRPM is responsible for the clinical activities in the CDRPM Health Screening Center. The following diagnostic imaging modalities are installed to facilitate high level of diagnostic accuracy: positron emission computed tomography (PET), 3-tesla magnetic resonance imaging (3T-MRI) system, multi-detector CT (MDCT), ultrasound imaging system, and digital mammography.

Teaching Activities

At present, CDRPM does not accept students. However, CDRPM participates in the education of students and residents in the Department of Radiology. CDRPM endeavors to help students whose research themes include image analysis such as computer-

assisted detection, or epidemiologic studies employing health-screening data.

Research Activities

1) Health screening database

We have developed a unique health screening information system to facilitate daily management of the health screening activities and to input health screening data. This information system is still under constant revision. The medical images acquired in the health screenings are stored in the hospital picture archiving and communication system (PACS) for clinical use. Medical images used solely for research purposes are stored in an independent PACS installed inside the CDRPM department.

2) Image processing software development

We have structured an integrated software developing system to facilitate the production of image processing software. The system is divided into the clinical part and the research part, with the data in the latter being anonymized. The clinical part consists of case entry for software development, and clinical application of the developed software. The research part consists of an interface to obtain images of the representative cases to develop the software, and an interface to test the developed software with the accumulated cases.

3) Clinical evaluation, application of software, and epidemiological studies

Researches based on the health-screening database are carried out in collaboration with other researchers of various specialties. Images are analyzed using the developed software.

References

- 1) Takahashi M, Takenaga T, Nomura Y, Hanakoka S, Hayashi N, Nemoto M, Nakao T, Miki S, Yoshikawa T, Kobayashi T, Abe S. Automated volume measurement of abdominal adipose tissue from entire abdominal cavity in dixon MR images using deep learning. *Radiol Phys Technol*. 2023;16(1):28-38. doi:10.1007/s12194-022-00687-x.
- 2) Ishii S, Hatano M, Maki H, Minatsuki S, Saito A, Yagi H, Shimbo M, Soma K, Numata G, Fujiwara T, Takeda N, Komura I. Prognostic value of follow-up vasoreactivity test in pulmonary arterial hypertension. *J Cardiol*. 2023. doi: 10.1016/j.jjcc.2023.01.005.
- 3) Kikuchi T, Hanaoka S, Nakao T, Nomura Y, Yoshikawa T, Alam A, Mori H, Hayashi N. Significance of FDG-PET standardized uptake values in predicting thyroid disease. *European Thyroid Journal*. 2023;12(1):e220165. doi: 10.1530/ETJ-22-0165.
- 4) Yoshikawa T, Miki S, Nakao T, Koshino S, Hayashi N, Abe O. Axillary lymphadenopathy after pfizer-BioNTech and moderna COVID-19 vaccination: MRI evaluation. *Radiology*. 2023; 306(1):270-278. doi: 10.1148/radiol.220814.
- 5) Sasako T, Kadowaki H, Fujiwara T, et al. Severe aortic stenosis during leptin replacement therapy in a patient with generalized lipodystrophy-associated progeroid syndrome due to an LMNA variant: A case report. *J Diabetes Investig*. 2022;13(9):1636-1638. doi: 10.1111/jdi.13827.
- 6) Shibata H, Hanaoka S, Nomura Y, Nakao T, Takenaga T, Hayashi N, Abe O. On the simulation of ultra-sparse-view and ultra-low-dose computed tomography with maximum a posteriori reconstruction using a progressive flow-based deep generative model. *Tomography (Ann Arbor)*. 2022;8(5):2129-2152. doi: 10.3390/tomography8050179.
- 7) Shimbo M, Hatano M, Ishii S, et al. Renal replacement therapy as a therapeutic option for right heart failure in severe pulmonary arterial hypertension. *ESC Heart Fail*. 2022;9(4):2728-2731. doi: 10.1002/ehf2.13945.
- 8) Nakao T, Hanaoka S, Nomura Y, Hayashi N, Abe O. Anomaly detection in chest 18F-FDG PET/CT by bayesian deep learning. *Jpn J Radiol*. 2022; 40(7):730-739. doi: 10.1007/s11604-022-01249-2.
- 9) Hoshiai S, Hanaoka S, Masumoto T, Nomura Y, et al. Effectiveness of temporal subtraction computed tomography images using deep learning in detecting vertebral bone metastases. *Eur J Radiol*. 2022;154:110445. doi: 10.1016/j.ejrad.2022.110445.
- 10) Itai S, Tonosaki K, Ono S, Watanabe R, Koshino S, et al. The inhibitory effect of catechin on the

growth of oral bacteria in vitro and halitosis in a clinical setting. . 2022;in press.

- 11) Nakayama A, Kodera S, Morita H, Fujiwara T, Takeda N, Komuro I. Cost-effectiveness of management for hospitalized patients; gender difference between female and male cardiologists. *International Heart Journal*. 2022;63(2):264-270. doi: 10.1536/ihj.21-451.
- 12) Yoshikawa M, Asaba K, Nakayama T. Estimating causal effects of genetically predicted type 2 diabetes on COVID-19 in the east asian population. *Front Endocrinol*. 2022;13. doi: 10.3389/fendo.2022.1014882.
- 13) Shimbo M, Amiya E, Komuro I. Telemonitoring during exercise training in cardiac telerehabilitation: A review. *Rev. Cardiovasc. Med*. 2023;. ;24(4). doi: 10.31083/j.rcm2404104.

Department of Home Care Medicine

Project Professor

Takashi Yamanaka, M.D., Ph.D.

Project Lecturer

Jiro Okochi, M.D., Ph.D.

Project Research Associate

Kiwami Kidana, M.D., Ph.D., Shota Hamada, R.Ph., Dr.P.H.

Homepage <http://chcm.umin.jp/>

Introduction and Organization

Department of Home Care Medicine was established in 2018 at the 22nd Century Medical and Research Center in the University of Tokyo Hospital. We have taken over educational activities and research activities from Center for Home Care Medicine, Faculty of Medicine.

With the increase in the elderly population, home care medicine is more needed compared with the past. We teach home care medicine to medical students and trainee doctors along with studying the topics of home care medicine to systematize it.

Education

Clinical education of home care medicine is provided for fifth and sixth year medical students. We create a personalized mandatory program of home care medicine and give an orientation of the program. Then medical students learn about home care medicine with physicians, nurses, medical social workers or care managers in the community.

We also create a program of home care medicine for trainee doctors who wish to learn about it.

Research

The main themes of our study were as follows.

- 1) Educational program development of home care medicine and studying the educational effectiveness of the program
- 2) Building a case registry system of home medical care
- 3) Follow-up study on QOL or prognosis of patients who receive home medical care and their care givers
- 4) Drug treatment in home medical care
- 5) Skills of medical therapeutics and care in home care medicine
- 6) Research on the construction of a digital platform for home care medicine

Publications

1. Hirakawa Y, Muraya T, Yamanaka T, Hirahara S, Okochi J, Kuzuya M, Miura H. Total pain in advanced dementia: a quick literature review. *J Rural Med.* 2023;18(2):154-158. doi: 10.2185/jrm.2022-007. Epub 2023 Apr 5. PMID: 37032982; PMCID: PMC10079462.
2. Hamada S, Iwagami M, Sakata N, Hattori Y, Kidana K, Ishizaki T, Tamiya N, Akishita M, Yamanaka T. Changes in Polypharmacy and Potentially Inappropriate Medications in Homebound Older Adults in Japan, 2015-2019: a Nationwide Study. *J Gen Intern Med.* 2023; 38(16):3517-3525. doi: 10.1007/s11606-023-

08364-4. Epub 2023 Aug 24. PMID: 37620717;
PMCID: PMC10713963.

Department of Therapeutic Strategy for Heart Failure

Research Associate Professor

Eisuke Amiya, M.D., Ph.D (2021/11/1-)

Research Assistant Professor

Seitaro Nomura, M.D., Ph.D(-2023/3/31)

Toshiyuki Ko, M.D., Ph.D (2021/11/1-)

Genri Numata, M.D., Ph.D(2023/4/1-)

Project Researcher

Naoko Kato, Ph.D

※The following information is the same as that of the previous year for certain reasons.

Homepage <http://plaza.umin.ac.jp/~heart-f/>

Introduction and Organization

The Department of Therapeutic Strategy for Heart Failure (TSHF) in the University of Tokyo Hospital was established by the support of the Department of Cardiac Surgery and the Department of Cardiovascular Medicine of the University of Tokyo Hospital in May 2008. The purpose to establish the department of TSHF is to promote surgical and medical innovative treatment for end-stage heart failure in the University of Tokyo Hospital, which includes heart transplant, pediatric heart transplant, ventricular assist device, and regenerative therapy. The Department has been also supported by eight companies.

Recently, right heart failure (RHF) gains recognition as well as left heart failure (LHF). RHF developed after left ventricular assist device (LVAD) is a critical issue which remains to be elucidated. Pulmonary hypertension (PH) is also an important cause of RHF. Now a lot of patients with severe PH are referred to our hospital because the University of Tokyo Hospital has

been approved as a lung transplantation center since 2014. We pursue optimal treatment strategy for not only LHF but also RHF.

Clinical Activities

1. Heart Transplant (HTx)

Patients who performed heart transplant in our hospital or in abroad transferred from our hospital are followed up once a month in the out-patient clinic, and undergo repeated myocardial biopsy regularly. When some symptom or findings which suggest rejection are detected, patients will undergo to intensify immunosuppressive regimen in-hospital treatment.

2. Ventricular Assist Device (VAD) Therapy

We recently implant not only extracorporeal pulsatile but also implantable ventricular assist device (VAD). All candidates fell into end-stage heart failure before VAD implantation, and a significant number of them were rescued with heart transplantation or bridge

to recovery. We implant centrifugal VAD (EVAHEART, HVAD and HeartMate3) or axial VAD (HeartMate II and Jarvik 2000) considering patients' physics and clinical status). We also started the "Destination therapy", which means the implantation of VAD without heart transplantation.

3. Treatment of PH

Although pulmonary arterial hypertension (PAH) was a disease of poor prognosis, the treatment outcome of PAH significantly improved in this decade attributed to a number of newly approved drugs. Now we can use ten agents for PAH including oral, inhaled, subcutaneous and intravenous drugs. Combination therapy of these drugs is increasingly prevalent for the management of PAH. We join the nationwide PH registry to establish optimal treatment strategy for PAH.

Teaching Activities

We have the chair of systematic review of cardiovascular surgery in the spring term at the 2nd grade of medical course. We also take charge in clinical practice on diagnosis of cardiovascular disease in the autumn term at the 2nd grade. We expose the students to daily clinical works as well as research works during the course of "Free Quarter" and "Research Lab Visit", which are scheduled in the summer and spring vacations at 1st and 2nd grade. Joint lectures with the Cardiology Department are scheduled 3rd through 4th grades. Each student is assigned one or two cardiovascular surgical cases in the Bed Side Learning, in which he/she is required to learn preoperative patient evaluation and management, surgical treatment and postoperative care, based on participatory practice. There are also twelve small key-lectures on cardiovascular surgery. Hands-on practice is provided during the "Clinical clerkship" one-month course in the last months of 3rd grade.

We take charge in core surgical curriculum in the "Super-rotation" postgraduate training. We offer a program in which each resident can learn basic knowledge of cardiovascular disease and surgery, and hemodynamic and respiratory evaluation as well as basic surgical techniques and patient management. Residents who take the course of cardiovascular surgery are required three-year general surgical

training for General Surgery Board certification. We have well-developed specialty/ subspecialty training programs to allow the residents to pass Cardiovascular Board Examination by 10th postgraduate year.

Research Activities

In order to achieve excellent clinical results and to seek for new possibilities of surgical treatments for heart failure, it is essential for our department of the University to have active research programs in clinical and basic subjects related to assisted circulations and heart transplantation. We created highly active research programs in every field of medical and surgical heart failure treatment, and played an internationally leading role and contributed to its development. A research meeting is held every Saturday on a research project with Department of Cardiothoracic Surgery.

Basic and/or clinical research activities are focused on 1) development of new driving method of rotary blood pump, 2) basic and clinical research on regenerative therapy, 3) establishment of social support system for patients with implantable LVAD.

References

- 1: Gyoten T, Amiya E, Ono M. Surgical Interventions for Late Aortic Valve Regurgitation Associated with Continuous Flow-Left Ventricular Assist Device Therapy: Experience Gained and Lessons Learned. *Life* (Basel). 2022 Dec 29;13(1):94.
- 2: Gyoten T, Amiya E, Kinoshita O, Tsuji M, Kimura M, Hatano M, Ono M. Clinical outcomes of continuous flow left ventricular assist device therapy as bridge to transplant strategy in muscular dystrophy: a single-center study. *Gen Thorac Cardiovasc Surg*. 2023 Jun;71(6):347-353.
- 3: Tsuji M, Kakuda N, Bujo C, Saito A, Ishida J, Amiya E, Hatano M, Shimada A, Imai H, Kimura M, Ando M, Kinoshita O, Yamauchi H, Komuro I, Ono M. Prophylactic negative pressure wound therapy is not effective for preventing driveline infection following left ventricular assist device implantation. *Artif Organs*. 2023 Mar;47(3):566-573.
- 4: Isotani Y, Amiya E, Ishida J, Komuro I. Summation of Precordial R Wave Amplitudes, a

- Clinical Parameter for Detecting Early TTR Amyloidosis Cardiac Involvement. *J Cardiovasc Dev Dis*. 2022 Oct 11;9(10):348.
- 5: Bujo S, Amiya E, Maeda MH, Ishida J, Hatano M, Ishizuka M, Uehara M, Oshima T, Kojima T, Nakanishi K, Daimon M, Shimizu J, Toda T, Komuro I. The effect of immunosuppressive therapy on cardiac involvements in anti-mitochondrial antibody-positive myositis. *ESC Heart Fail*. 2022 Dec;9(6):4112-4119.
 - 6: Ishizuka M, Uehara M, Katagiri M, Ishida J, Kojima T, Amiya E, Komuro I. Successful treatment of recurrent cardiac sarcoidosis with the combination of corticosteroid and methotrexate monitored by 18F-fluoro-2-deoxyglucose positron emission tomography: case series. *Eur Heart J Case Rep*. 2022 Aug 12;6(8):ytac334.
 - 7: Amiya E, Morita H. Simple Way of Identifying High-Risk Group of Heart Failure in Hypertrophic Cardiomyopathy in the Japanese Population. *Circ J*. 2022 Nov 25;86(12):1941-1942.
 - 8: Kakuda N, Amiya E, Hatano M, Tsuji M, Bujo C, Ishida J, Yagi H, Saito A, Narita K, Isotani Y, Fujita K, Ando M, Shimada S, Kinoshita O, Ono M, Komuro I. Residual Pulmonary Vascular Resistance Increase Under Left Ventricular Assist Device Support Predicts Long-Term Cardiac Function After Heart Transplantation. *Front Cardiovasc Med*. 2022 Jun 1;9:904350.
 - 9: Ko T, Nomura S, Yamada S, Fujita K, Fujita T, Satoh M, Oka C, Katoh M, Ito M, Katagiri M, Sassa T, Zhang B, Hatsuse S, Yamada T, Harada M, Toko H, Amiya E, Hatano M, Kinoshita O, Nawata K, Abe H, Ushiku T, Ono M, Ikeuchi M, Morita H, Aburatani H, Komuro I. Cardiac fibroblasts regulate the development of heart failure via Htra3-TGF- β -IGFBP7 axis. *Nat Commun*. 2022 Jun 7;13(1):3275.
 - 10: Narita K, Amiya E, Hatano M, Ishida J, Minatsuki S, Tsuji M, Bujo C, Kakuda N, Isotani Y, Ono M, Komuro I. Determining the factors for interhospital transfer in advanced heart failure cases. *Int J Cardiol Heart Vasc*. 2022 May 14;40:101035.
 - 11: Yagi H, Takeda N, Amiya E, Akiyama N, Chang H, Ishiura H, Sato J, Akazawa H, Morita H, Komuro I. Nonsyndromic arteriopathy and aortopathy and vascular Ehlers-Danlos syndrome causing COL3A1 variants. *Am J Med Genet A*. 2022 Sep;188(9):2777-2782.
 - 12: Gyoten T, Amiya E, Kinoshita O, Tsuji M, Kimura M, Hatano M, Ono M. Myocardial recovery evaluation from ventricular assist device in patients with dilated cardiomyopathy. *ESC Heart Fail*. 2022 Aug;9(4):2491-2499.
 - 13: Shimbo M, Hatano M, Ishii S, Saito A, Yagi H, Minatsuki S, Maki H, Amiya E, Takeda N, Komuro I. Renal replacement therapy as a therapeutic option for right heart failure in severe pulmonary arterial hypertension. *ESC Heart Fail*. 2022 Aug;9(4):2728-2731.
 - 14: Amiya E. Social Inequalities in Non-ischemic Cardiomyopathies. *Front Cardiovasc Med*. 2022 Mar 7;9:831918. doi: 10.3389/fcvm.2022.831918.
 - 15: Isotani Y, Amiya E, Ishida J, Ishizuka M, Hatano M, Nakanishi K, Daimon M, Komuro I. Recovery of sinus rhythm by tafamidis in patients with wild-type transthyretin amyloid cardiomyopathy with atrial arrhythmias. *Oxf Med Case Reports*. 2022 Feb 19;2022(2):omac007.
 - 16: Tsuji M, Kakuda N, Bujo C, Ishida J, Amiya E, Hatano M, Shimada A, Imai H, Shimada S, Kinoshita O, Yamauchi H, Ono M, Komuro I. Sarcopenia and risk of infection in adult heart transplant recipients in Japan. *ESC Heart Fail*. 2022 Apr;9(2):1413-1423.
 - 17: Hatano M, Jimba T, Fujiwara T, Tsuji M, Bujo C, Ishida J, Amiya E, Kinoshita O, Ono M. Late-onset right ventricular failure after continuous-flow left ventricular assist device implantation: case presentation and review of the literature. *J Cardiol*. 2022 Aug;80(2):110-115.
 - 18: Shoji S, Kuno T, Kohsaka S, Amiya E, Asleh R, Alvarez P, Kampaktsis P, Staffa SJ, Zurakowski D, Doulamis I, Briasoulis A. Incidence and long-term outcome of heart transplantation patients who develop postoperative renal failure requiring dialysis. *J Heart Lung Transplant*. 2022 Mar;41(3):356-364.
 - 19: Sugihara T, Nakaoka Y, Uchida HA, Yoshifuji H, Maejima Y, Watanabe Y, Amiya E, Tanemoto K, Miyata T, Umezawa N, Manabe Y, Ishizaki J, Shirai T, Nagafuchi H, Hasegawa H, Miyamae T, Nihiro H, Ito S, Ishii T, Isobe M, Harigai M.

Establishing clinical remission criteria and the framework of a treat-to-target algorithm for Takayasu arteritis: Results of a Delphi exercise carried out by an expert panel of the Japan Research Committee of the Ministry of Health, Labour and Welfare for intractable vasculitis. *Mod Rheumatol*. 2022 Aug 20;32(5):930-937.

- 20: Narita K, Amiya E. Social and environmental risks as contributors to the clonal course of heart failure. *Heart Fail Rev*. 2022 Jul;27(4):1001-1016.

Department of Biostatistics and Bioinformatics

Project Professor

Daisuke Koide, R.Ph., HIM, Ph.D.

Project Lecturer

Shogo Nomura, Ph.D.

Project Assistant Professor

Shotaro Aso, MD, Ph.D .

Homepage <http://biostatistics.m.u-tokyo.ac.jp/>

Introduction and Organization

Biostatistics is an applied statistics in the fields of medical and health sciences and contributes to these fields through developments of statistical methodologies for clinical trials and epidemiological researches. Biostatisticians who work at an organization for conducting and coordinating clinical researches (e.g., academic research organization) in hospitals and institutions are few in Japan. To this end, the Japan funding agency, Agency for Medical Research and Development (AMED), started the Support Program for Biostatisticians from 2016.

The AMED selected the Graduate School of the University of Tokyo and the Graduate school of the Kyoto University, as 2 centers for training biostatisticians, which function as core facilities, respectively. Each graduate school establishes a new biostatistics course, forms a training center upon collaboration with a hospital, and performs on-the-job training.

This program improves the environment that leads to higher quality in clinical research and trials, with the collaboration of industry, academia, and the government, based upon the donations from drug companies and national research funding. Collaborative projects of industry, academia, and the government through the flow of funds in this program, are the first of their kind in Japan.

On March 1, 2017, the Department of Biostatistics

and Bioinformation was established in the Graduate School of Medicine. In the Graduate School of Interdisciplinary Information Studies in the University of Tokyo, the Biostatistics and Bioinformatics course also started on April 1, 2018. This course provides specialized education to acquire not only statistical methodologies, but also practical skills (e.g., design and analysis of clinical research, programming, reporting) for conducting clinical research. We train biostatisticians with high communication skill and ethics that can promote high quality research in collaboration with health care professionals by teaching and on-the-job -training (OJT). AMED has renewed this project for more 5years since FY2021.

Teaching activities

1) Education in the Biostatistics and Bioinformatics course

In the Biostatistics and Bioinformatics course, through the following teachings, we educate a wide range of knowledge and skills required to biostatisticians. Its curriculum is made up of 28 subjects including 42 credits. For students who have taken over 38 credits, we issue a certificate along with the Master degree.

Biostatistics

Statistical inference, categorical data analysis,

survival analysis, longitudinal data analysis, Bayesian statistics, multiple comparison procedure, multivariate analysis, causal inference, missing data analysis, stochastic process and time series analysis, pharmacometrics, statistical programming, genomic data analysis

Clinical research and epidemiology

Clinical trial methodology, design and analysis of epidemiological research, research ethics and guidelines, medical research and CDISC standards, general clinical medicine, regulatory science, medical writing, medical technology evaluation exercises

In addition, the students receive the OJT at University of Tokyo Hospital and the National Cancer Center. The OJT programs are developed by the biostatisticians of each institution. In the first year of master's program, the students learn the basic practice of biostatistician through the training at the University of Tokyo Hospital. In the second year, at the National Cancer Research Center, students receive advanced training in how to plan the design and analysis of clinical researches.

2) Seminars and symposiums for the healthcare professionals and biostatisticians

We give seminars about clinical trial methodologies and biostatistics for physician, nurse, clinical research coordinator, monitor, and other healthcare professionals. We also hold symposia for biostatisticians in academia and pharmaceutical companies in order to share and discuss the “state-of-the-arts” of statistical methodologies.

Research activities

In the department of biostatistics and bioinformatics, the main research areas are as follows:

1) Statistical methodology and design of clinical trials and epidemiology

We study on the statistical methodologies and design for streamlining clinical trial and estimating treatment effect precisely. The research area includes Bayesian design in oncology, clinical trial design using biomarkers, adaptive design, study on the use of

Bayesian statistics in clinical trials, causal inference, and multiple comparison method.

2) Epidemiological methodology

Epidemiology deals with health or disease related incidence quantitatively in large populations, evaluates cause and effective factors, and ultimately finds the measures of prevention. It starts from epidemics (such as infectious diseases) and now its focus is on lifestyle related diseases, such as cardiovascular disorders. Also, several kinds of medical databases are developed rapidly in Japan. It is important to conduct epidemiological, pharmacoepidemiological and clinical epidemiological studies using such databases.

3) Pharmacoepidemiology

Pharmacoepidemiology is a study to investigate drug use and its effects in a population. We are engaged in research on effectiveness, risk, and cost using data obtained from hospital information system and electronic medical record.

4) Clinical Epidemiology

Clinical epidemiology is the application of the principles and methods of epidemiology to conduct clinical research studies focusing on prevention, diagnosis, prognosis, and treatment of disease. As the basic science of Evidence-based Medicine, the importance of clinical epidemiology has been increasing.

5) Medical informatics

Medical informatics is a science of studying how to use data, information and knowledge in the all medical fields, such as clinical, medical studies, education and government. Recently, the area of medical informatics is much expanding because of the progress of genomic studies or bioinformatics, and introduction of new technologies, such as virtual reality and artificial intelligence (AI).

6) Algebraic statistics

The focus of research is on developing and applying methods of algebraic statistics to specific statistical problems. In statistical inference, the computation of complicated integrals or summation sometimes makes the problem intractable. When a statistical model

has algebraic structure, techniques from algebraic statistics are useful. I currently work on the topics related to Groebner basis theory and the holonomic gradient method.

References

1. Facile R, Muhlbradt EE, Gong M, Li Q, Popat V, P?avy F, Cornet R, Ruan Y, Koide D, Saito TI, Hume S, Rockhold F, Bao W, Dubman S, Jauregui Wurst B. Use of Clinical Data Interchange Standards Consortium (CDISC) Standards for Real-world Data: Expert Perspectives From a Qualitative Delphi Survey. *JMIR Med Inform.* 2022 Jan 27;10(1):e30363. doi: 10.2196/30363. PMID: 35084343; PMCID: PMC8832264.
2. Nishikawa A, Yoshinaga E, Nakamura M, Suzuki M, Kido K, Tsujimoto N, Ishii T, Koide D. Validation Study of Algorithms to Identify Malignant Tumors and Serious Infections in a Japanese Administrative Healthcare Database. *Annals of Clinical Epidemiology.* 4(1): 20-31. 2022. Doi: <https://doi.org/10.37737/ace.22004>
3. Nakachi K, Ikeda M, Konishi M, Nomura S, Katayama H, Kataoka T, Todaka A, Yanagimoto H, Morinaga S, Kobayashi S, Shimada K, Takahashi Y, Nakagohri T, Gotoh K, Kamata K, Shimizu Y, Ueno M, Ishii H, Okusaka T, Furuse J, Hepatobiliary and Pancreatic Oncology Group of the Japan Clinical Oncology G. Adjuvant S-1 compared with observation in resected biliary tract cancer (JCOG1202, ASCOT): a multicentre, open-label, randomised, controlled, phase 3 trial. *Lancet.* 2023. 401(10372): 195-203.
4. Nakamura Y, Okamoto W, Denda T, Nishina T, Komatsu Y, Yuki S, Yasui H, Esaki T, Sunakawa Y, Ueno M, Shinozaki E, Matsushashi N, Ohta T, Kato K, Ohtsubo K, Bando H, Hara H, Satoh T, Yamazaki K, Yamamoto Y, Okano N, Terazawa T, Kato T, Oki E, Tsuji A, Horita Y, Hamamoto Y, Kawazoe A, Nakajima H, Nomura S, Mitani R, Yuasa M, Akagi K and Yoshino T. Clinical Validity of Plasma-Based Genotyping for Microsatellite Instability Assessment in Advanced GI Cancers: SCRUM-Japan GOZILA Substudy. *JCO Precis Oncol.* 2022. 6: e2100383.
5. Morizane C, Machida N, Honma Y, Okusaka T, Boku N, Kato K, Nomura S, Hiraoka N, Sekine S, Taniguchi H, Okano N, Yamaguchi K, Sato T, Ikeda M, Mizuno N, Ozaka M, Kataoka T, Ueno M, Kitagawa Y, Terashima M, Furuse J and Japan Clinical Oncology G. Effectiveness of Etoposide and Cisplatin vs Irinotecan and Cisplatin Therapy for Patients With Advanced Neuroendocrine Carcinoma of the Digestive System: The TOPIC-NEC Phase 3 Randomized Clinical Trial. *JAMA Oncol.* 2022. 8(10): 1447-1455.
6. Terashima T, Morizane C, Ushima M, Shiba S, Takahashi H, Ikeda M, Mizuno N, Tsuji K, Yasui K, Azemoto N, Satake H, Nomura S, Yachida S, Sugano K and Furuse J. Germline variants in cancer-predisposing genes in pancreatic cancer patients with a family history of cancer. *Jpn J Clin Oncol.* 2022. 52(10): 1105-1114.
7. Niguma K, Mamishin K, Naito Y, Nomura S, Wakabayashi M, Kusuha S, Funasaka C, Nakao T, Fukasawa Y, Kondoh C, Harano K, Kogawa T, Matsubara N, Hosono A, Onishi T, Kawasaki T and Mukohara T. Impact of Older Age and Medico-social Factors on the Decision to Offer Adjuvant Chemotherapy to Patients With Breast Cancer. *Anticancer Res.* 2022. 42(7): 3743-3751.
8. Hasegawa H, Tsukada Y, Wakabayashi M, Nomura S, Sasaki T, Nishizawa Y, Ikeda K, Takeshita N, Teramura K and Ito M. Impact of near-infrared fluorescence imaging with indocyanine green on structural sequelae of anastomotic leakage after laparoscopic intersphincteric resection of malignant rectal tumors. *Tech Coloproctol.* 2022. 26(7): 561-570.
9. Kojima T, Kato K, Hara H, Takahashi S, Muro K, Nishina T, Wakabayashi M, Nomura S, Sato A, Ohtsu A and Doi T. Phase II study of BKM120 in patients with advanced esophageal squamous cell carcinoma (EPOC1303). *Esophagus.* 2022. 19(4): 702-710.
10. Aso S, Ono S, Michihata N, Uemura K, Yasunaga H. Effectiveness of vaccination on influenza-related critical illnesses in the elderly population. *J Infect Chemother.* 2023;S1341-321X(23)00037-5.

Department of Advanced Cardiology

Project Associate Professor

Katsuhito Fujiu, M.D., Ph.D.

Project Lecturer

Hidehiro Kaneko, M.D., Ph.D.

Project Assistant Professor

Ying Chen, M.D., Ph.D.

※The following information is the same as that of the previous year for certain reasons.

Homepage <https://cardiovasc.m.u-tokyo.ac.jp/>

Introduction and Organization

This course is an endowed chair established on April 1, 2018, under the donations of Medtronic Japan Co., Ltd., St. Jude Medical Co., Ltd., Boston Scientific Japan Co., Ltd., Fukuda Denshi Tokyo Central Sales Co., Ltd and SIMPLEX QUANTUM Co., Ltd.

In conjunction with the department of cardiovascular medicine, this course develops leading-edge medical care. It elucidates the pathogenesis of unresolved heart failure and cardiovascular disease and analyzes the pathological condition using cultured cells, experimental animals, and patient specimens. By clarifying the new disease pathogenesis mechanism and pathogenesis mechanism, it aims at elucidating the fundamental pathophysiology of cardiovascular disease and developing development prevention methods, new diagnostic methods, and new therapeutic methods.

Teaching activities

The above research results are presented at the university and academic conferences, the importance of this field is well known and widely presented by dissertation. Also, we are actively engaged in outreach activities for society.

Research activities

The heart and blood vessels maintain homeostasis in cooperation with organs throughout the body. The failure of this cooperation is considered to cause the onset of heart failure and sudden death. The therapy that improved cardiovascular death prognosis is a drug that acts on the whole body, not on the heart alone, except for cardiac resynchronization therapy and implantable defibrillator. From this point of view, as a research to improve the prognosis of cardiovascular death, we will proceed with the investigation, considering that poor coordination among multiple organs is involved in the onset of heart disease. Furthermore, about half of the cells that make up the heart are cardiomyocytes. In contrast, the other half are non-cardiomyocytes. In this study, we focus on non-cardiomyocytes and how non-cardiomyocytes interact with cardiomyocytes. The aim is to find new therapeutic targets for heart disease by clarifying whether it is acting, maintaining homeostasis of the heart, and elucidating the pathogenesis of heart failure that is its failure.

Furthermore, the relationship between the heart and the brain has been examined in detail as a study of inter-organ cooperation.

References

1. Age Modified Relationship Between Modifiable Risk Factors and the Risk of Atrial Fibrillation. Matsuoka S, Kaneko H, Okada A, Morita K, Itoh H, Michihata N, Jo T, Takeda N, Morita H, Fujiu K, Nakamura S, Node K, Yasunaga H, Komuro I. *Circ Arrhythm Electrophysiol*. 2022 Jan;15(1): e010409. doi: 10.1161/CIRCEP.121.010409.
2. Nerve-macrophage interactions in cardiovascular disease. Fujiu K, Manabe I. *Int Immunol*. 2022 Jan 22; 34(2): 81-95. doi: 10.1093/intimm/dxab 036.
3. Deep learning model to detect significant aortic regurgitation using electrocardiography. Sawano S, Kodera S, Katsushika S, Nakamoto M, Ninomiya K, Shinohara H, Higashikuni Y, Nakanishi K, Nakao T, Seki T, Takeda N, Fujiu K, Daimon M, Akazawa H, Morita H, Komuro I. *J Cardiol*. 2022 Mar;79(3):334-341. doi: 10.1016/j. jjcc.2021.08.029.
4. Acute-Phase Initiation of Cardiac Rehabilitation for Short-Term Improvement in Activities of Daily Living in Patients Hospitalized for Acute Heart Failure. Ueno K, Kamiya K, Kaneko H, Okada A, Itoh H, Fujiu K, Takeda N, Morita H, Michihata N, Jo T, Yasunaga H, Komuro I. *J Cardiovasc Dev Dis*. 2022 Mar 25;9(4):97. doi: 10.3390/jcdd9040097.
5. Change in Cardiovascular Health Metrics and Risk for Proteinuria Development: Analysis of a Nationwide Population-Based Database. Suzuki Y, Kaneko H, Okada A, Itoh H, Morita K, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Yamaguchi S, Kamiya K, Matsunaga A, Ako J, Fukui A, Nishiyama A, Yokoo T, Node K, Yamauchi T, Nangaku M, Yasunaga H, Komuro I. *Am J Nephrol*. 2022; 53(2-3): 240-248. doi: 10.1159/000522147. <2022.4>
6. Risk for Proteinuria in Newly Defined Hypertensive People Based on the 2017 American College of Cardiology/American Heart Association Blood Pressure Guideline. Suzuki Y, Kaneko H, Okada A, Itoh H, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Yamaguchi S, Yano Y, Kamiya K, Matsunaga A, Ako J, Fukui A, Yokoo T, Nishiyama A, Node K, Yamauchi T, Nangaku M, Yasunaga H, Komuro I. *Am J Cardiol*. 2022 Apr 1;168:83-89. doi: 10.1016/j. amjcard.2021.12.023.
7. Association between proteinuria and incident colorectal cancer: analysis of a nationwide population-based database. Matsuoka S, Kaneko H, Okada A, Fukui A, Yano Y, Itoh H, Morita K, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Yamaguchi S, Nakamura S, Nishiyama A, Yokoo T, Node K, Yamauchi T, Nangaku M, Yasunaga H, Komuro I. *BMJ Open*. 2022 Apr 4;12(4):e056250. doi: 10.1136/bmjopen-2021-056250.
8. Relationship of normal-weight central obesity with the risk for heart failure and atrial fibrillation: analysis of a nationwide health check-up and claims database. Ueno K, Kaneko H, Kamiya K, Itoh H, Okada A, Suzuki Y, Matsuoka S, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Ako J, Node K, Yamauchi T, Yasunaga H, Komuro I. *Eur Heart J Open*. 2022 Apr 13; 2(3): oeac026. doi: 10.1093/ehjopen/oeac 026.
9. Impact of Glucose Tolerance and Its Change on Incident Proteinuria: Analysis of a Nationwide Population-Based Dataset. Suzuki Y, Kaneko H, Okada A, Itoh H, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Yamaguchi S, Kamiya K, Matsunaga A, Ako J, Node K, Yamauchi T, Nangaku M, Yasunaga H, Komuro I. *Am J Nephrol*. 2022; 53(4): 307-315. doi: 10.1159/ 000522280. <2022.5>
10. Prediction of Atrial Fibrillation Being Asymptomatic at First Onset by Cardiac Pacing. Matsubara TJ, Fujiu K, Kodera S, Kani K, Goto K, Shimizu Y, Oguri G, Hasumi E, Kojima T, Komuro I. *Int Heart J*. 2022;63(3):486-491. doi: 10.1536/ihj.21-594. <2022.5>
11. Association of retinal atherosclerosis assessed using Keith-Wagener-Barker system with incident heart failure and other atherosclerotic cardiovascular disease: Analysis of 319,501 individuals from the general population. Matsuoka S, Kaneko H, Okada A, Itoh H, Suzuki Y, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Nakamura S, Node K, Yasunaga H, Komuro I. *Atherosclerosis*. 2022 May; 348: 68-74. doi: 10.1016/j.atherosclerosis.2022.02.024.

12. Age-Dependent Relationship of Hypertension Subtypes With Incident Heart Failure. Suzuki Y, Kaneko H, Yano Y, Okada A, Itoh H, Matsuoka S, Fujiu K, Yamaguchi S, Michihata N, Jo T, Takeda N, Morita H, Node K, Kim HC, Viera AJ, Oparil S, Yasunaga H, Komuro I. *J Am Heart Assoc*. 2022 May 3;11(9):e025406. doi: 10.1161/JAHA.121.025406.
13. Comparison of cardiovascular outcomes between SGLT2 inhibitors in diabetes mellitus. Suzuki Y, Kaneko H, Okada A, Itoh H, Matsuoka S, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Kamiya K, Matsunaga A, Ako J, Node K, Yasunaga H, Komuro I. *Cardiovasc Diabetol*. 2022 May 18;21(1):67. doi: 10.1186/s12933-022-01508-6.
14. Prediabetes in Young Adults and Its Association With Cardiovascular Health Metrics in the Progression to Diabetes. Suzuki Y, Kaneko H, Okada A, Matsuoka S, Itoh H, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Yamaguchi S, Node K, Yamauchi T, Yasunaga H, Komuro I. *J Clin Endocrinol Metab*. 2022 Jun 16;107(7):1843-1853. doi: 10.1210/clinem/dgac247.
15. Clinical utility of simple subjective gait speed for the risk stratification of heart failure in a primary prevention setting. Ueno K, Kaneko H, Kamiya K, Itoh H, Okada A, Suzuki Y, Matsuoka S, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Ako J, Yasunaga H, Komuro I. *Sci Rep*. 2022 Jul 8; 12(1):11641. doi: 10.1038/s41598-022-13752-7.
16. Medication-Naïve Blood Pressure and Incident Cancers: Analysis of 2 Nationwide Population-Based Databases. Kaneko H, Yano Y, Lee HH, Lee H, Okada A, Itoh H, Morita K, Fukui A, Fujiu K, Suzuki Y, Matsuoka S, Nakamura S, Michihata N, Jo T, Takeda N, Morita H, Yokoo T, Nishiyama A, Node K, Viera AJ, Muntner P, Oparil S, Kim HC, Yasunaga H, Komuro I. *Am J Hypertens*. 2022 Aug 1;35(8): 731-739. doi: 10.1093/ajh/hpac054.
17. Rivaroxaban Monotherapy vs Combination Therapy With Antiplatelets on Total Thrombotic and Bleeding Events in Atrial Fibrillation With Stable Coronary Artery Disease: A Post Hoc Secondary Analysis of the AFIRE Trial. Naito R, Miyauchi K, Yasuda S, Kaikita K, Akao M, Ako J, Matoba T, Nakamura M, Hagiwara N, Kimura K, Hirayama A, Matsui K, Ogawa H; AFIRE Investigators. *JAMA Cardiol*. 2022 Aug 1;7(8): 787-794. doi: 10.1001/jamacardio.2022.1561.
18. Effectiveness and Approach of Rehabilitation in Patients With Acute Heart Failure: A Review. Ueno K, Kaneko H, Itoh H, Takeda N, Morita H, Fujiu K, Kamiya K, Komuro I. *Korean Circ J*. 2022 Aug;52(8):576-592. doi: 10.4070/kcj.2022.0181.
19. Cholecystitis and Cholangitis during Continuous Renal Replacement Therapy in a Patient with Retroperitoneal Hemorrhage Requiring Large Amounts of Contrast Medium for the Assessment and Intervention. Goto K, Shimizu Y, Kojima T, Takeda N, Fujiu K, Komuro I. *Intern Med*. 2022 Aug 15; 61(16): 2533-2537. doi: 10.2169/internalmedicine.8518-21.
20. Age-Specific Relation of Cardiovascular Health Metrics With Incident Cardiovascular Disease. Itoh H, Kaneko H, Okada A, Suzuki Y, Fujiu K, Matsuoka S, Michihata N, Jo T, Nakanishi K, Takeda N, Morita H, Node K, Di Tullio MR, Homma S, Yasunaga H, Komuro I. *Am J Cardiol*. 2022 Aug 15;177:34-39. doi: 10.1016/j.amjcard.2022.04.046.
21. Semiquantitative assessed proteinuria and risk of heart failure: analysis of a nationwide epidemiological database. Fukui A, Kaneko H, Okada A, Yano Y, Itoh H, Matsuoka S, Morita K, Kiriya H, Kamon T, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Nakamura S, Nishiyama A, Node K, Yokoo T, Nangaku M, Yasunaga H, Komuro I. *Nephrol Dial Transplant*. 2022 Aug 22;37(9):1691-1699. doi: 10.1093/ndt/gfab248.
22. Non-Cardiac Organs Metamorphose Heart.
23. Oshima T, Fujiu K. *Int Heart J*. 2022;63(5): 795-797. doi: 10.1536/ihj.22-403. <2022.9>
24. Automatic Detection of Left Ventricular Dilatation and Hypertrophy from Electrocardiograms Using Deep Learning. Kokubo T, Koder S, Sawano S, Katsushika S, Nakamoto M, Takeuchi H, Kimura N, Shinohara H, Matsuoka R, Nakanishi K, Nakao T, Higashikuni Y, Takeda N, Fujiu K, Daimon M, Akazawa H, Morita H, Matsuyama Y, Komuro I. *Int Heart J*. 2022 Sep 30;63(5):939-947. doi: 10.1536/ihj.22-132.

25. Incorporation of Retinal Arteriolosclerosis into Risk Stratification of Blood Pressure Category According to the 2017 ACC/AHA Blood Pressure Guideline. Matsuoka S, Kaneko H, Kamon T, Suzuki Y, Yano Y, Okada A, Itoh H, Morita K, Fukui A, [Fujiu K](#), Michihata N, Jo T, Takeda N, Morita H, Nakamura S, Yokoo T, Nishiyama A, Node K, Yasunaga H, Komuro I. *J Atheroscler Thromb*. 2022 Oct 1; 29(10):1487-1498. doi: 10.5551/jat.63262.
26. Sex Difference in the Association between Lipid Profile and Incident Cardiovascular Disease among Young Adults. Kamon T, Kaneko H, Itoh H, Okada A, Matsuoka S, Kiriyaama H, [Fujiu K](#), Morita K, Michihata N, Jo T, Takeda N, Morita H, Nakamura S, Node K, Yasunaga H, Komuro I. *J Atheroscler Thromb*. 2022 Oct 1;29(10):1475-1486. doi: 10.5551/jat.63166.
27. Association of Cardiovascular Health Metrics With Risk of Transition to Hypertension in Non-Hypertensive Young Adults. Suzuki Y, Kaneko H, Yano Y, Okada A, Itoh H, Matsuoka S, [Fujiu K](#), Michihata N, Jo T, Takeda N, Morita H, Matsunaga A, Node K, McEvoy JW, Lam CSP, Oparil S, Yasunaga H, Komuro I. *Am J Hypertens*. 2022 Oct 3; 35(10):858-866. doi: 10.1093/ajh/hpac057.
28. Reduction in blood pressure for elevated blood pressure/stage 1 hypertension according to the American College of Cardiology/American Heart Association guideline and cardiovascular outcomes. Kaneko H, Yano Y, Suzuki Y, Okada A, Itoh H, Matsuoka S, [Fujiu K](#), Michihata N, Jo T, Takeda N, Morita H, Node K, Viera AJ, Lima JAC, Oparil S, Lam CSP, Carey RM, Yasunaga H, Komuro I. *Eur J Prev Cardiol*. 2022 Oct 20; 29(14):1921-1929. doi: 10.1093/eurjpc/zwac193.
29. Age prediction from coronary angiography using a deep neural network: Age as a potential label to extract prognosis-related imaging features. Sawano S, Kodera S, Sato M, Katsushika S, Sukeda I, Takeuchi H, Shinohara H, Kobayashi A, Takiguchi H, Hirose K, Kamon T, Saito A, Kiriyaama H, Miura M, Minatsuki S, Kikuchi H, Higashikuni Y, Takeda N, [Fujiu K](#), Ando J, Akazawa H, Morita H, Komuro I. *PLoS One*. 2022 Oct 27; 17(10):e0276928. doi: 10.1371/journal.pone.0276928. eCollection 2022.
30. Kidney outcomes in patients with diabetes mellitus did not differ between individual sodium-glucose cotransporter-2 inhibitors.
31. Suzuki Y, Kaneko H, Okada A, Matsuoka S, [Fujiu K](#), Michihata N, Jo T, Takeda N, Morita H, Node K, Nangaku M, Yasunaga H, Komuro I. *Kidney Int*. 2022 Nov; 102(5):1147-1153. doi: 10.1016/j.kint.2022.05.031. Epub 2022 Aug 9.
32. Is Continuous Monitoring for Arrhythmia Advantageous in Low-Risk Groups? Matsubara TJ, [Fujiu K](#). *JACC Asia*. 2022 Nov 1;2(6):747-749. doi:10.1016/j.jacasi.2022.09.004. eCollection 2022 Nov.
33. Threshold of BMI for the Development of Hypertension among Japanese Adults. Suzuki Y, Kaneko H, Yano Y, Okada A, Hashimoto Y, Itoh H, Matsuoka S, Yokota I, [Fujiu K](#), Michihata N, Jo T, Takeda N, Morita H, Kamiya K, Matsunaga A, Ako J, Node K, Yasunaga H, Komuro I. *J Nutr*. 2022 Nov;152(11):2565-2571. doi: 10.1093/jn/nxac192. Epub 2022 Aug 30.
34. Glycemic status and the association of change in blood pressure with incident cardiovascular disease. Suzuki Y, Kaneko H, Yano Y, Okada A, Itoh H, Matsuoka S, [Fujiu K](#), Michihata N, Jo T, Takeda N, Morita H, Kamiya K, Matsunaga A, Ako J, Node K, Yasunaga H, Komuro I. *Am Heart J*. 2022 Dec;254:48-56. doi: 10.1016/j.ahj.2022.07.005. Epub 2022 Jul 22.
35. Deep learning-based age estimation from chest X-rays indicates cardiovascular prognosis. Ieki H, Ito K, Saji M, Kawakami R, Nagatomo Y, Takada K, Kariyasu T, Machida H, Koyama S, Yoshida H, Kurosawa R, Matsunaga H, Miyazawa K, Ozaki K, Onouchi Y, Katsushika S, Matsuoka R, Shinohara H, Yamaguchi T, Kodera S, Higashikuni Y, [Fujiu K](#), Akazawa H, Iguchi N, Isobe M, Yoshikawa T, Komuro I. *Commun Med (Lond)*. 2022 Dec 9; 2(1):159. doi: 10.1038/s43856-022-00220-6.
36. Association of Life's Simple 7 with incident cardiovascular disease in 53 974 patients with cancer. Kaneko H, Suzuki Y, Ueno K, Okada A, [Fujiu K](#), Matsuoka S, Michihata N, Jo T, Takeda N, Morita H, Kamiya K, Node K, Yasunaga H, Komuro I. *Eur J Prev Cardiol*. 2022 Dec 21;

-
- 29(18):2324-2332. doi: 10.1093/eurjpc/zwac195.
37. Dose-dependent relationship of blood pressure and glycaemic status with risk of aortic dissection and aneurysm. Suzuki Y, Kaneko H, Yano Y, Okada A, Itoh H, Ueno K, Matsuoka S, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Yokota I, Node K, Yasunaga H, Komuro I. Eur J Prev Cardiol. 2022 Dec 21;29(18):2338-2346. doi: 10.1093/eurjpc/zwac205.
38. Proteinuria and Risk for Heart Failure in 55,191 Patients Having History of Cancer. Suzuki Y, Kaneko H, Okada A, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Kamiya K, Matsunaga A, Ako J, Node K, Nangaku M, Yasunaga H, Komuro I. Am J Nephrol. 2022;53(10):753-760. doi: 10.1159/000527703. Epub 2022 Dec 21. < 2023.1 >

Department of Advanced Clinical Science and Therapeutics

Project Associate Professor

Mutsuo Harada, M.D., Ph.D.

Project Assistant Professor

Masamichi Ito, M.D., Ph.D.

Project Researcher

Yusuke Adachi, M.D., Ph.D.

Satoshi Bujo, M.D., Ph.D.

Project Academic Support Staff

Kanako Ikeya,

Yuko Ishiyama

Introduction and Organization

The Department of Advanced Clinical Science and Therapeutics, established at the University of Tokyo in 2004, aims to develop new clinical strategies and therapy in cardiovascular medicine and other areas. The laboratory location was moved to the brand new research building called Clinical Research Center-A in January 2020. This department hopes to develop not only basic research, but also applications to devise new clinical strategies.

Research activities

Followings are our recent basic and clinical research activities.

- New strategies to regulate acute/chronic myocarditis.
- New strategies to regulate acute myocardial infarction and ischemia/reperfusion injury.
- New strategies to regulate atherosclerosis and aneurism.
- New strategies to regulate systolic/diastolic heart failure.

- New strategies to regulate cardio-kidney syndrome.
- Development of gene therapies with AAV vectors (anti-inflammation etc.).
- Development of new growth factor treatments (hepatocyte growth factor, etc.).
- Development of new anti-adhesion molecule treatments (anti-inflammation, etc.).
- Development of new anti-extracellular treatments (anti-inflammation, anti-oxidation, etc.).
- Development of new chemical compounds (anti-inflammation, anti-coagulation, etc.).
- Development of drug screening for heart failure using iPS cell-derived cardiomyocytes.
- Expanding the use of foods and natural extracts.
- Expanding the application of existing drugs and devices.
- Analysis of angiogenesis using in situ hybridization.

References

1. Miyazawa K, Ito K, Ito M, Zou Z, Kubota M, Nomura S, Matsunaga H, Koyama S, Ieki H, Akiyama M, Koike Y, Kurosawa R, Yoshida H,

- Ozaki K, Onouchi Y; BioBank Japan Project; Takahashi A, Matsuda K, Murakami Y, Aburatani H, Kubo M, Momozawa Y, Terao C, Oki S, Akazawa H, Kamatani Y, Komuro I. Cross-ancestry genome-wide analysis of atrial fibrillation unveils disease biology and enables cardioembolic risk prediction. *Nat Genet.* 2023 Feb;55(2):187-197.
2. Bujo S, Toko H, Ito K, Koyama S, Ishizuka M, Umei M, Yanagisawa-Murakami H, Guo J, Zhai B, Zhao C, Kishikawa R, Takeda N, Tsushima K, Ikeda Y, Takimoto E, Morita H, Harada M, Komuro I. Low-carbohydrate diets containing plant-derived fat but not animal-derived fat ameliorate heart failure. *Sci Rep.* 2023 Mar 9; 13(1):3987.
 3. Yamada S, Ko T, Ito M, Sassa T, Nomura S, Okuma H, Sato M, Imasaki T, Kikkawa S, Zhang B, Yamada T, Seki Y, Fujita K, Katoh M, Kubota M, Hatsuse S, Katagiri M, Hayashi H, Hamano M, Takeda N, Morita H, Takada S, Toyoda M, Uchiyama M, Ikeuchi M, Toyooka K, Umezawa A, Yamanishi Y, Nitta R, Aburatani H, Komuro I. TEAD1 trapping by the Q353R-Lamin A/C causes dilated cardiomyopathy. *Sci Adv.* 2023 Apr 14;9(15):eade7047.
 4. Adachi Y, Ueda K, Takimoto E. Perivascular adipose tissue in vascular pathologies-a novel therapeutic target for atherosclerotic disease? *Front Cardiovasc Med.* 2023 May 26;10:1151717
 5. Yamada T, Nomura S, Amiya E, Katoh M, Inoue S, Hatsuse S, Fujita K, Ito M, Fujita T, Bujo C, Tsuji M, Ishida J, Ko T, Yamada S, Katagiri M, Sassa T, Kinoshita O, Nawata K, Tobita T, Satoh M, Ishiwata J, Daimon M, Tatsuno K, Fukuda S, Kashimura T, Minamino T, Hatano M, Ono M, Aburatani H, Komuro I. LMNA Mutations and Right Heart Failure in Patients With Cardiomyopathy and With Left Ventricular Assist Devices. *J Card Fail.* 2023 May;29(5):855-857.
 6. Fujiwara T, Takeda N, Hara H, Ishii S, Numata G, Tokiwa H, Katoh M, Maemura S, Suzuki T, Takiguchi H, Yanase T, Kubota Y, Nomura S, Hatano M, Ueda K, Harada M, Toko H, Takimoto E, Akazawa H, Morita H, Nishimura S, Komuro I. PGC-1 α -mediated angiogenesis prevents pulmonary hypertension in mice. *JCI Insight.* 2023 Sep 8;8(17):e162632.
 7. Candray-Medina KS, Nakagama Y, Ito M, Nakagama S, Tshibangu-Kabamba E, Takeda N, Sugiura Y, Nitahara Y, Michimuko-Nagahara Y, Kaku N, Onizuka Y, Arias CE, Mejia M, Alas K, Peña S, Maejima Y, Komuro I, Nakajima-Shimada J, Kido Y. Differential cardiomyocyte transcriptomic remodeling during in vitro *Trypanosoma cruzi* infection using laboratory strains provides implications on pathogenic host responses. *Trop Med Health.* 2023 Dec 7;51(1): 68.

Department of Comprehensive Radiation Oncology

Project Professor

Keiichi Nakagawa, MD, Ph.D

Project Research Associate

Masanari Minamitani, MD, Ph.D

Academic Specialist

Shingo Ohira, Ph.D

Homepage <http://www.u-tokyo-rad.jp/staff/shuyougakukouza.html>

Introduction and Organization

The endowed chair was launched on April 1, 2021. At the time of its establishment, there were two members: project professor Nakagawa and project associate Ozaki. Due to Ozaki's appointment at Hirosaki University, on April 1, 2022, Minamitani joined as a project associate. In April 2023, Ohira was appointed as an academic specialist.

The purpose of the establishment of this course is to: From the standpoint of clinical radiation oncology and medical physics, (1) promote the development of radiation therapy technology, (2) train medical physicists with science and engineering backgrounds and promote the precision of radiation therapy, (3) improve the public's literacy about cancer in general with a focus on radiation therapy (including medical physics and the effects of radiation on the human body), and (4) "cancer education" described in the Course of Study for junior high and high schools in particular. We are supporting the promotion of the four of them. We have received support from Elekta K.K. and Chiyoda Technol Corporation.

Nakagawa is the former head of the Radiation Therapy Division. While researching the development of radiation therapy equipment and clinical applications, he felt the importance of specialists in medical physics. Currently, medical physicists are working at relatively large hospitals that perform

radiation therapy, but the development of bases for medical physicists has not progressed. One of the primary goals of this course is to contribute to the further development of medical physics through the improvement of image quality related to radiation therapy, the analysis of big data in the field of radiation therapy, and the development of human resources in collaboration with the Radiation Therapy Division.

In addition, Nakagawa was involved in the launch of the Basic Act on Cancer Control enacted in 2006 and served as a member of the Council for the Promotion of Cancer Control for ten years. It has aimed to improve public cancer education and Japanese people's health literacy by doing so. Improving health literacy using cancer teaching materials leads to various benefits in society, such as cancer prevention and early detection, patient-centered decision-making when selecting treatment methods, balancing cancer treatment and work, and social understanding of the effects of radiation on the human body. Our second goal is to become a base for these issues.

Clinical activities

Two LINACs, one Tomotherapy, one iridium brachytherapy device, one gamma knife for stereotactic irradiation of the head, one CT imaging device dedicated to treatment planning, and treatment planning devices are equipped in the Department of

Radiation Oncology. The primary purpose of this course is not clinical. Still, we assist in medical treatment while examining cases with doctors in the treatment department as appropriate.

In addition, feedback on issues recognized in clinical practice is received and linked to technological development.

Education

This course provides graduate school education to students from the Graduate School of Medicine, Faculty of Medicine, the University of Tokyo. The Department also collaborates with the Graduate Schools of Science and Engineering and accepts students from science and engineering backgrounds who wish to become medical physicists and research students conducting medical physics research.

While there were no admissions of students aspiring to be medical physicists in 2023, we are expanding the educational structure in preparation for accepting students from 2024 onwards. Additionally, seven students from the Department of Radiology and Biomedical Engineering are affiliated with the radiation therapy department, and guidance has been provided for tasks such as thesis writing.

Research

Following the purpose of this course, we conduct research on medical physics and cancer education. In medical physics, we are developing new high-precision radiation therapy technologies by researching "image-guided radiation irradiation methods" using images related to radiation therapy and research on image processing utilizing artificial intelligence and analysis of big data related to radiation therapy in collaboration with related clinical departments.

For example, in a study to predict the effect of radiotherapy for pancreatic cancer, the contrast agent (iodine) uptake of the tumor was quantitatively analyzed by Dual-energy CT (DECT). Pancreatic cancer is one of the poorest prognostic cancers. It has become clear that high doses of radiation for pancreatic cancer can provide favorable therapeutic effects. However, high-dose administration is risky because of the location of radiosensitive and dangerous organs such as the stomach and duodenum around the pancreas.

If we can identify patients with poor response before radiotherapy, we may be able to administer high doses only to the group of patients with poor response. Postoperative pathological specimen analysis of cases treated with preoperative radiotherapy revealed that the greater the difference in iodine uptake between the pancreatic parenchyma and the pancreatic tumor, the poorer the histopathological treatment effect[5]. Future research should combine our findings with artificial intelligence to improve the accuracy of predicting treatment efficacy.

In school education for cancer, Nakagawa received a Grant for Scientific Research on "Development and Evaluation of Teaching Materials for Cancer Education on Radiotherapy", and Minamitani received a Grant on "Research on Mid- and Long-term Evaluation of Cancer Education in Curricula"[3]. In August, Nakagawa and Minamitani made a presentation at the general meeting of the Diet Members Association for Cancer Education, and Minamitani also made a presentation on cancer education at a lecture meeting on health education held by the Tokyo Metropolitan Government Education Agency. In addition, research on the evaluation of medical students' practice of cancer education for children as service learning has begun. This is a two-sided study of health education and medical education.

For adult cancer education, within the Corporate Action to Promote Cancer Control, a commissioned project by the Ministry of Health, Labour, and Welfare chaired by Nakagawa, both Nakagawa and Minamitani have provided lectures to corporations both online and offline. Minamitani is making efforts to improve cancer control in the workplace and in the community as a co-researcher of the "Research on Social Implementation of Science-Based Cancer Screening in the Workplace," a project funded by the Ministry of Health, Labor and Welfare's Science Research Grant, and as a member of the Arakawa Ward Health Promotion Plan Formulation Committee.

As mentioned above, our department conducts extensive research activities in both medical physics and cancer education. Coupled with talent development, we look forward to further progress in the next fiscal year.

Publications

- 1: Katano A, Minamitani M, Yamashita H, Nakagawa K. National Survey of Radiotherapy Utilization Trends from 2015 to 2019, Based on the National Database of Health Insurance Claims and Specific Health Checkups of Japan. *JMA J.* 2023;6(3):342-345.
- 2: Atsuto Katano, Yuki Nozawa, Masanari Minamitani, Hideomi Yamashita, Keiichi Nakagawa. Novel breath-hold liver target stereotactic ablative radiotherapy using the intrafraction diaphragm registration of kilovoltage projection streaming image with digitally reconstructed radiography of the planning computed tomography. *Technical Innovations and Patient Support in Radiation Oncology*, 2023; 27: 100217
- 3: Masanari Minamitani, Atsuto Katano, Keiichi Nakagawa. Assessing the effectiveness of a school educational video on cancer and radiotherapy. *Health Education Journal* 2023; 82:820–833
- 4: Katano A, Minamitani M, Shingo Ohira, Yamashita H. Failure Patterns of Recurrence in Patients With Localized Esthesioneuroblastoma Following Surgery and Adjuvant Radiotherapy Without Elective Nodal Irradiation. *Cureus.* 2023; 15: e46523
- 5: Shingo Ohira, Toshiki Ikawa, Naoyuki Kanayama, Masanari Minamitani, Sayaka Kihara, Shoki Inui, Yoshihiro Ueda, Masayoshi Miyazaki, Hideomi Yamashita, Teiji Nishio, Masahiko Koizumi, Keiichi Nakagawa, Koji Konishi, Dual-energy computed tomography-based iodine concentration as a predictor of histopathological response to preoperative chemoradiotherapy for pancreatic cancer, *Journal of Radiation Research.* 2023; 64: 940–947.
- 6: Atsuto Katano, Yuki Nozawa, Masanari Minamitani, Shingo Ohira, Keiichi Nakagawa. Intrafractional Diaphragm Variations During Breath-Hold Stereotactic Body Radiotherapy for a Liver Tumor Based on Real-Time Registration Between Kilovoltage Projection Streaming and Digitally Reconstructed Radiograph Images: A Case Report. *Cureus.* 2023; 15: e48188
- 7: Katano A, Minamitani M, Gao Tongyu, Shingo Ohira, Yamashita H. Survival Following Palliative Radiotherapy for Head and Neck Squamous Cell Carcinoma: Examining Treatment Indications in Elderly Patients. *Cancer diagnosis & prognosis.* 2023;4(1):46-50.
- 8: Katano A, Minamitani M, Shingo Ohira, Yamashita H. Recent Advances and Challenges in Stereotactic Body Radiotherapy. *Technology in cancer research & treatment.* 2023; 23: 15330338241229363- 15330338241229363.
- 9: Atsuto Katano, Yuki Kasuga, Shingo Ohira, Masanari Minamitani, Hideomi Yamashita. Hypofractionated Radiotherapy as a Standalone Treatment Modality for Locally Advanced Type B2 Thymoma in an Octogenarian Patient: 45 Gy in 15 Fractions. *Cureus.* 2023; 16: e51528
- 10: Atsuto Katano, Masanari Minamitani, , Shingo Ohira, Hideomi Yamashita. Curative Radiotherapy for Oropharyngeal Squamous Cell Carcinoma Stratified by p16 Status, According to the Eighth Edition American Joint Committee on Cancer Staging Manual: A Retrospective Study. *Cancer diagnosis & prognosis.* 2024; 4: 117-121.

Department of Immunotherapeutics

Project Professor

Kazuhiro Kakimi, M.D.,Ph.D.

Project Lecturer

Koji Nagaoka, Ph.D.

Project Researcher

Yukari Kobayashi

Technical Assistant

Yaeko Furuhashi, Yukiko Konakai

※The following information is the same as that of the previous year for certain reasons.

Homepage <https://immunotherapy-uth.jp/>

Introduction and Organization

The Department of Immunotherapeutics is located within the 22nd Century Medical and Research Center, established in 2004 within the University of Tokyo Hospital as a base for industry-academia collaboration and as an organization promoting translational research. It was established to conduct clinical research and clarify the role of this treatment technology in cancer treatment.

In May 2019, MEDINET Co., Ltd. completed the endowed courses for three periods of 15 years, and from June, Takara Bio Co., Ltd. made a new start as endowed courses. The laboratory location has also moved from the Central Clinical Building II to the Molecular Life Innovation Building. We conduct several joint programs with many clinical departments and engage in research on tumor immunology by analyzing the obtained clinical specimens with cutting-edge technology.

Our goal is to build a system that integrates a huge amount of clinical data and provides optimal treatment for each patient. In particular, we are focusing on identifying neoantigens based on patient genome

information and developing TCR-T cell therapy using neoantigen-specific TCRs.

Teaching activities

Graduate students from the department of Neurosurgery, Gastroesophageal Surgery, Respiratory Surgery, and Urology joined our team for research. We collected surgically resected tumors from each clinical department, cultured tumor-infiltrating lymphocytes, extracted DNA/RNA from the tumors, and performed NGS analysis. We are studying the effects of the intratumoral immune environment on anti-tumor immune responses

In the laboratory, in addition to basic immunoassay techniques using cell culture and flow cytometry, they have mastered the handling of bioinformatics tools necessary for genome analysis.

Graduate students who are actually in charge of outpatient care or endoscopies in their respective clinical departments, or with the help of colleagues, build cooperation with medical offices and affiliated hospitals, collect specimens, and conduct research. I believe that this experience will help them develop

new treatment methods and tackle unknown issues when they become future clinical practice leaders.

Three graduate students who published papers on research using valuable specimens before and after treatment with immune checkpoint inhibitors, searching for biomarkers that predict postoperative prognosis, and researching neoantigen immunotherapy using mouse models, successfully obtained a Ph.D. degree.

Research activities

Immune checkpoint inhibitors have been approved for various cancer types, but many patients still do not respond to these therapies or become resistant to them after therapeutic effects have been shown. In order to rationally judge the indications of immune checkpoint inhibitors and clarify the points of resistance to treatment, we will clarify the molecular mechanisms that determine the responsiveness to immune checkpoint inhibitors in individual patients.

Accumulated clinical experience defines responsiveness to immune checkpoint inhibitors, including tumor-specific factors, tumor microenvironment, host-related factors, and dynamic changes associated with treatment. Furthermore, high-dimensional analysis at the single-cell level becomes possible, and it is possible and necessary to comprehensively integrate detailed and enormous information for predicting efficacy and searching for the key to overcoming treatment resistance.

We have studied current tumor immunology based on detailed observations, accumulating hypotheses and their verification. On the other hand, in genomic analysis, comprehensive information is searched for answers without being bound by preconceptions using bioinformatics and computer science. To have confidence in evaluating the anti-tumor immune response, we should integrate conventional immunology and genomic immunology. Therefore, tumor immunology research conducted in our department focuses on integrative analysis as cancer immunogenomics.

NGS has allowed it to analyze neoantigens generated from genomic abnormalities in individual patients, enabling the development of cancer immunotherapy

targeting neoantigens.

Neoantigens are predicted based on genomic information of individual patients by the high binding ability to MHC molecules. Then, they are validated for their reactivity to tumor-specific T cells.

Therefore, we constructed an innovative neoantigen analysis platform that combines a neoantigen prediction system and immunogenicity verification using tumor-specific TCR-expressing cells. Our goal is to realize TCR-T cell therapy targeting neoantigens.

Publication List

1. Ishii T, Mimura I, Nagaoka K, Naito A, Sugawara T, Kuroda R, Yamada D, Kanki Y, Kume H, Ushiku T, Kakimi K, Tanaka T, Nangaku M. Effect of M2-like macrophages of the injured-kidney cortex on kidney cancer progression. *Cell Death Discov.* 2022 Dec 5;8(1):480. doi: 10.1038/s41420-022-01255-3. PMID: 36470862; PMCID: PMC9722672.
2. Sun C, Nagaoka K, Kobayashi Y, Maejima K, Nakagawa H, Nakajima J, Kakimi K. Immunotherapies targeting neoantigens are effective in PD-1 blockade-resistant tumors. *Int J Cancer.* 2023 Apr 1;152(7):1463-1475. doi: 10.1002/ijc.34382. Epub 2022 Dec 13. PMID: 36451303.
3. Teshima T, Kobayashi Y, Kawai T, Kushiara Y, Nagaoka K, Miyakawa J, Akiyama Y, Yamada Y, Sato Y, Yamada D, Tanaka N, Tsunoda T, Kume H, Kakimi K. Principal component analysis of early immune cell dynamics during pembrolizumab treatment of advanced urothelial carcinoma. *Oncol Lett.* 2022 Jun 16;24(2):265. doi: 10.3892/ol.2022.13384. PMID: 35765279; PMCID: PMC9219027.
4. Miyamoto A, Honjo T, Masui M, Kinoshita R, Kumon H, Kakimi K, Futami J. Engineering Cancer/Testis Antigens With Reversible S-Cationization to Evaluate Antigen Spreading. *Front Oncol.* 2022 May 4;12:869393. doi: 10.3389/fonc.2022.869393. PMID: 35600379; PMCID: PMC9115381.
5. Saito N, Sato Y, Abe H, Wada I, Kobayashi Y, Nagaoka K, Kushiara Y, Ushiku T, Seto Y, Kakimi K. Selection of RNA-based evaluation

methods for tumor microenvironment by comparing with histochemical and flow cytometric analyses in gastric cancer. *Sci Rep.* 2022 May 20;12(1):8576. doi:10.1038/s41598-022-12610-w. PMID: 35595859.

6. Sato S, Matsushita H, Shintani D, Kobayashi Y, Fujieda N, Yabuno A, Nishikawa T, Fujiwara K, Kakimi K, Hasegawa K. Association between effector-type regulatory T cells and immune checkpoint expression on CD8⁺ T cells in malignant ascites from epithelial ovarian cancer. *BMC Cancer.* 2022 Apr 21;22(1):437. doi: 10.1186/s12885-022-09534-z. PMID: 35449092; PMCID: PMC9026673.

Social Cooperation Program

Department of Medical Information Engineering

Project Associate Professor

Taichi Kin, M.D.,Ph.D.

Project Research Associate

Toki Saito, Ph.D.

※The following information is the same as that of the previous year for certain reasons.

Homepage <https://medicalinfo-engineering.org>

Introduction and Organization

Department of Medical Information Engineering was launched on November 2021, through the financial support of SoftBank corporation, with assistance by the Department of Neurosurgery. Two faculty staffs, Taichi Kin as the Specially Appointed Associate Professor and Toki Saito as the Specially Appointed Assistant Professor started the research project.

The Department of Medical Information Engineering aims at research and development of medical data processing such as medical images by making full use of information and communication technology, artificial intelligence technology, anonymous processing technology, and cloud technology. Specifically, this includes medical image processing technologies such as tissue segmentation, annotation, and virtual reality surgical simulation, and anonymization, information and communication technologies of medical image data.

Teaching activities

Department of Medical Information Engineering was involved in the education through research activities of graduate students of the Graduate School of Medicine.

Research activities

Our research covers the biomedical computer applications that focus on medical data such as medical imaging. Our laboratory is engaged in the following research activities:

- 1) medical image processing
3D reconstruction, segmentation, registration, rendering, fluid dynamics
- 2) virtual reality surgical simulation
tissue deformation, using surgical instruments
- 3) surgical support system
surgical navigation, XR technology
- 4) information and communication technology
block chain, anonymization, cloud technology

References

1. Satoshi Kiyofuji, Taichi Kin, Toki Saito, Tsukasa Koike, Yasuhiro Takeda, Tatsuya Uchida, Katsuya Sato, Ryoko Niwa, Yasuyuki Furuta, Nobuhito Saito. Invention of Online Interactive Three-dimensional Neurosurgery Simulator with Audiovisual Capture for Tactile Feedback. *Oper Neurosurg.* 24(2): 194-200, 2022.
2. Tsukasa Koike, Shota Tanaka, Taichi Kin, Yuichi Suzuki, Shunsaku Takayanagi, Hirokazu Takami, Kazuha Kugasawa, Shohei Nambu, Takaki Omura Erika Yamazawa Yoshihiro Kushihara, Yasuyuki Furuta, Ryoko Niwa, Katsuya Sato,

- Tatsuya Uchida, Yasuhiro Takeda, Satoshi Kiyofuji, Toki Saito, Hiroshi Oyama, Nobuhito Saito. Accurate Preoperative Identification of Motor Speech Area as Termination of Arcuate Fasciculus Depicted by Q-Ball Imaging Tractography. *World Neurosurg* 164: e764-e771, 2022.
3. Yuki Shinya, Masahiro Shin, Hirotaka Hasegawa, Satoshi Koizumi, Taichi Kin, Kenji Kondo, Nobuhito Saito. Endoscopic endonasal transpetroclival approach for recurrent bilateral petroclival meningioma. *Neurosurg Focus Video* 6(2): v7, 2022.
4. Hirotaka Hasegawa, Masahiro Shin, Ryoko Niwa, Satoshi Koizumi, Shoko Yoshimoto, Naoyuki Shono, Yuki Shinya, Hirokazu Takami, Shota Tanaka, Umekawa Motoyuki, Shiori Amemiya, Taichi Kin, Nobuhito Saito. Revisitation of imaging features of skull base chondrosarcoma in comparison to chordoma. *J Neurooncol* 159(3): 581-590, 2022.
5. Takeda Yasuhiro, Hasegawa Hirotaka, Kin Taichi, Shinya Yuki, Kawashima Mariko, Furuta Yasuyuki, Suzuki Yuichi, Sekine Tetsuro, Saito Nobuhito. Hemodynamic changes during the obliteration process for cerebralarteriovenous malformations after radiosurgery. *Neurosurg Focus* 53(1): E7, 2022.
6. Nozomi Otsuka, Hirohisa Yajima, Satoru Miyawaki, Satoshi Koizumi, Satoshi Kiyofuji, Hiroki Hongo, Yu Teranishi, Taichi Kin, Nobuhito Saito. Case Report: "Clipping" an Internal Carotid Artery Aneurysm With a Duplicated Middle Cerebral Artery and the Anterior Choroidal Artery Arising From the Dome. *Front Neurol* 13: 845296, 2022.
7. Yuki Shinya, Masahiro Shin, Hirotaka Hasegawa, Satoshi Koizumi, Taichi Kin, Kenji Kondo, Nobuhito Saito. Endoscopic endonasal transpetroclival approach for recurrent bilateral petroclival meningioma. *Neurosurg Focus Video* 6(2): V7, 2022.
8. Takeo Igarashi, Tsukasa Koike, Taichi Kin. Interactive Deformable Image Registration with Dual Cursor. DOI: 10.2312/pg.20221241. Pacific Graphics 2022.
9. Shono Naoyuki, Igarashi Takeo, Kin Taichi, Toki Saito, Nobuhito Saito. Threshold field painting saves the time for segmentation of minute arteries. *Int J Comput Assist Radiol Surg*. 17(11): 2121-2130, 2022.
10. Ding Xia, Xi Yang, Oliver van Kaick, Taichi Kin, Takeo Igarashi. Data-driven Multi-Modal Partial Medical Image Preregistration by Template Space Patch Mapping. *MICCAI 2022*, 259-268.
11. Hirohisa Yajima, Satoru Miyawaki, Satoshi Koizumi, Satoshi Kiyofuji, Hiroki Hongo, Masafumi Segawa, Taichi Kin, Hirofumi Nakatomi, Nobuhito Saito. Development of a sigmoid sinus dural arteriovenous fistula secondary to sigmoid sinus thrombosis after resection of a foramen magnum meningioma: illustrative case. *J Neurosurg Case Lessons* 4(5): CASE22253, 2022.
12. Kiyofuji Satoshi, Shin Masahiro, Kondo Kenji, Kin Taichi, Uchida Tatsuya, Saito Nobuhito. Endoscopic Transnasal Resection of Trigeminal Schwannoma. *J Neurol Surg B Skull Base* 83(Suppl 3): e637-e638, 2022.

Health Economy and Society Policy

Project Professor

Tomoyuki Takura, Ph.D, MEng.

Project Lecturer

Sayaka Horiuchi, MPH, MD

※The following information is the same as that of the previous year for certain reasons.

Homepage <http://plaza.umin.ac.jp/hehp/>

Introduction and Organization

Health Economy and Society policy is a donated fund course established in 22nd Century Medical and Research Center in February 2017, which is donated by 10 companies, Development Bank of Japan Inc., Chugai Pharmaceutical Co., Ltd., Baxter Limited, Nihon Medi-Physics Co., Ltd., Medibrain Corporation, Asahi Kasei Medical Co., Ltd., NIPRO Corporation, Toray Medical Co., Ltd., JMS Co., Ltd., and Terumo Corporation, and is cooperating with Department of Cardiac Surgery, Division of Nephrology and Endocrinology, and Department of Clinical Epidemiology & Health Economics as cooperating course.

The social structure has been changing over recent years and it can be assumed that policies related to the medical system and medical industry are at a crossroads in Japan and may undergo dramatic changes in the future. Our department was established to discuss future healthcare systems (medical practices and systems, economy and industry), particularly in terms of theory construction and validation studies pertaining to the "evaluation of the value of the healthcare field" and other topics. Concretely, we promote theoretical and methodological research on health technology assessment, cost effectiveness analysis, and the healthcare industry structure, and aim to evaluate the value of healthcare technologies and healthcare systems.

Education

We also promote manpower training programs (Program for "The movements of medical value": 18 times in total) in health technology assessment with collaboration departments, which is an extension course. This program includes healthcare economics (pharmaceutical affairs system, financial and insurance system, hospital accounting, cost-effectiveness evaluation, microeconomics) and data science (medical big data, bayesian statistics, markov chain monte carlo method, software analysis) and research ethics.

Research activities

We are engaging in the following research in order to promote rational and evidence-based medical resource investment, to support medical practice, and to promote advances in medical technology.

- 1) The evaluation of the cost effectiveness of various therapies, including (but not limited to) VAD therapy for severe heart failure, hemodialysis therapy for end-stage renal failure and radiological diagnostics.
- 2) A study of the socioeconomic impact of chronic pain and health behavior (adherence) on the disease burden and the financial burden (including international comparison).
- 3) Testing and developing methods for evaluating labor productivity (e.g., the productivity of cardiology

doctors) by applying data envelopment analysis (DEA) techniques.

Moreover, we are also working on a project to develop a forecasting model for health technology assessment (HTA) and disease prevention that makes use of big data and AI as data science. We have also started a study that applies computational finance to forecast the market value of research and development projects.

References

1. Tomoyuki Takura, Kosaku Nitta, Ken Tsuchiya, Hideki Kawanishi. Long-Term Effects of Contrast Media Exposure on Renal Failure Progression: A Retrospective Cohort Study. *BMC Nephrology*. 24, 135. 2023.
2. Tomoyuki Takura, Minoru Ono, Junya Ako, Yuji Ikari, Koichi Toda, Yoshiki Sawa; ETICA Study Investigators. Clinical and Economic Evaluation of Impella Treatment for Fulminant Myocarditis - A Preliminary Retrospective Cohort Study in Japan. *Circ J*. 2022; 87(5):610-618. doi: 10.1253/circj.CJ-22-0439.
3. Hiroki Sugimori, Maki Hirao, Ataru Igarashi, Hiroshi Yatsushashi, Shunya Ikeda, Naohiko Masaki, Hiroshi Yotsuyanagi, Takeshi Yoda, Takeshi Odajima, Tomoyuki Takura, Tomohiro Hirao. Health state utilities of patients with hepatitis B and C and hepatitis-related conditions in Japan. *Sci Rep*. 12(1):17139. 2022. doi: 10.1038/s41598-022-21470-3.
4. Tetsuya Shiina, Keiko Goto-Hirano, Tomoyuki Takura, Hiroyuki Daida. Cost-effectiveness of follow-up invasive coronary angiography after percutaneous coronary stenting: a real-world observational cohort study in Japan. *BMJ Open*. 12(8):e061617. 2022. doi: 10.1136/bmjopen-2022-061617.
5. Tomoyuki Takura, Sayaka Horiuchi. Cost-effectiveness analysis of infliximab for the treatment of Kawasaki disease refractory to the initial treatment: A retrospective cohort study. *Journal of Cardiology*. 80(2):172-178. doi: 10.1016/j.jjcc.2022.03.005. 2022.
6. Tomoyuki Takura, Hiroko Miura. Socioeconomic Determinants of Universal Health Coverage in the Asian Region. *Int. J. Environ. Res. Public Health*. 2022; 19(4):2376. <https://doi.org/10.3390/ijerph19042376>.
7. Tomoyuki Takura, Tomoko Koike, Yoko Matsuo, Asuko Sekimoto, Masami Mutou. Proxy Responses Regarding Quality of Life of Terminal Lung Cancer Patients: preliminary results from a prospective observational study. *BMJ Open*. 12(2):e048232. doi: 10.1136/bmjopen-2020-048232. 2022.
8. Kazuhiko Ikeuchi, Kazuya Okushin, Makoto Saito¹, Eisuke Adachi¹, Takeya Tsutsumi, Tomoyuki Takura, Hiroshi Yotsuyanagi. Prevalence of HIV infection among non-elderly individuals with hepatitis C in Japan: A population-based cohort study using a health insurance claim data. *BMC Infectious Diseases*. 22(1):167. doi: 10.1186/s12879-022-07152-5.2022.
9. Yasunori Suematsu, Shin-ichiro Miura, Akira Minei, Yoko Sumita, Koshiro Kanaoka, Michikazu Nakai, Hisatomi Arima, Koshi Nakamura, Tomoyuki Takura, Kazunori Shimada, Hirokazu Shiraishi, Nagaharu Fukuma, Yusuke Ohya, Shigeru Makita. Study Protocol of Cardiac Rehabilitation for Acute Myocardial Infarction From the JROAD/JROAD-DPC Database — JROAD-CR —. *The JROAD-CR Investigators. Circulation Reports*. 5 (2): 62-65. 2023.
10. JCS/JACR 2021 Guideline on Rehabilitation in Patients With Cardiovascular Disease. Shigeru Makita, Takanori Yasu, Yoshihiro J Akashi, Hitoshi Adachi, Hideo Izawa, Shunichi Ishihara, Yoshitaka Iso, Hideo Ohuchi, Kazuto Omiya, Yusuke Ohya 0, Koichi Okita, Yutaka Kimura, Akira Koike, Masahiro Kohzuki, Shinji Koba, Masataka Sata, Kazunori Shimada, Tomoki Shimokawa, Hirokazu Shiraishi, Naokata Sumitomo 0, Tetsuya Takahashi, Tomoyuki Takura, Hiroyuki Tsutsui, Masatoshi Nagayama, Emiko Hasegawa, Yoshihiro Fukumoto, Yutaka Furukawa, Shin-Ichiro Miura, Satoshi Yasuda, Sumio Yamada 0, Yuichiro Yamada, Dai Yumino, Toshiko Yoshida, Takuji Adachi, Toshimi Ikegame, Kazuhiro P Izawa, Takeshi Ishida, Neiko Ozasa, Naohiko Osada, Hiroaki Obata 0, Naoya Kakutani,

Yusuke Kasahara, Masaaki Kato, Kentaro Kamiya, Shintaro Kinugawa, Yuji Kono, Yasuyuki Kobayashi, Teruyuki Koyama, Kazuhiro Sase, Shinji Sato O, Tatsuhiko Shibata, Norio Suzuki, Daisuke Tamaki, Minako Yamaoka-Tojo, Michio Nakanishi, Eisaku Nakane, Mari Nishizaki, Taiki Higo, Kanta Fujimi, Tasuku Honda, Yasuharu Matsumoto, Noriko Matsumoto, Ikuko Miyawaki, Makoto Murata, Shusuke Yagi, Masanobu Yanase O, Midori Yamada, Miho Yokoyama, Noboru Watanabe, Haruki Ito, Takeshi Kimura, Syunei Kyo, Yoichi Goto, Ryuji Nohara, Ken-Ichi Hirata ; Japanese Circulation Society/the Japanese Association of Cardiac Rehabilitation Joint Working Group. *Circ J.* 2022 Dec 9. doi: 10.1253/circj.CJ-22-0234. Online ahead of print.

11. Tomoyuki Takura, Issei Komuro, Minoru Ono. Trends in the cost-effectiveness level of percutaneous coronary intervention: Macro socioeconomic analysis and health technology assessment. *J Cardiol.* 2022;81(4):356-363. Sep 28;S0914-5087(22)00243-X. doi: 10.1016/j.jjcc.2022.09.011. Online ahead of print.
12. Tomoyuki Takura. "Socio-Economic Considerations of Universal Health Coverage: Focus on the Concept of Health Care Value and Medical Treatment Price". *Health Insurance*. London, IntechOpen; 1-34. 2022 (DOI: 10.5772/intechopen.104798)

Department of Healthcare Quality Assessment

Project Professor

Hiroaki Miyata, PhD

Project Associate Professor

Hiraku Kumamaru, MD, ScD, Hiroyuki Yamamoto, MD, PhD, MPH

Project Assistant Professor

Naoaki Ichihara, MD, PhD, MPH

Project Researcher

Shun Kosaka, MD, PhD, Shiori Nishimura, PhD, Hisateru Tachimori, PhD,
Ryo Nakamaru, MD, PhD, Shiyori Usune

Visiting Researcher

Arata Takahashi, HIM, PhD, Hideki Endo, MD, Chieko Fujimura, Satoshi Shoji, MD, PhD
Shinya Hirakawa, PhD, Naoko Kinukawa, PhD, Daisuke Shinjo, PhD

Clerical Staff (Secretary)

Takayo Nakamura, Yuko Miyashiro

※The following information is the same as that of the previous year for certain reasons.

Website <http://hqa.umin.jp/>

Introduction and Organization

The Department of Healthcare Quality Assessment (HQA) was established in 2006, and now work in collaboration with the Departments of Cardiovascular Surgery, Health and Social Behavior, and Pediatric Surgery. It conducts collaborative research with National Clinical Database (NCD), Nipro Corporation, Johnson and Johnson K.K., and Intuitive Surgical Sàrl.

The objective of providing healthcare is to provide high quality healthcare services to all patients. Institute of Medicine states that health care reform should focus on improving the patients' health as well as health care values that they think are important. "Quality improvement initiative," therefore, needs to adjust the healthcare systems to accommodate the fee-for-service perspectives while

improving the clinical environment for both patients and providers.

Research

Department of Healthcare Quality Assessment (HQA) has been actively collaborating with healthcare professionals and various clinical committees as they play key roles in the quality improvement initiatives in the field. In such positive environment driven by the patient-centered philosophy, the patients receive more satisfying care, physicians are rewarded for their excellence, and healthcare costs are sustained. To accomplish these goals, there are 3 principles that navigate us through the journey: (a) the topmost value should always be on that of patients, (b) all medical practices should be organized around medical conditions as well as

the care cycles of the patients, and (c) the results---risk-adjusted outcomes and medical costs spent---must be scientifically measured and evaluated.

In April 2010, the Japan Society of Surgery and 10 related surgical societies founded the National Clinical Database (NCD), which is an all-Japan endeavor that aims to build a large-scale, comprehensive clinical registry that utilize the “big data” to improve the quality of surgery as well as advance surgical sciences in Japan. HQA has been playing important academic roles in the project since its birth. The actual data entry started from January 1st, 2011, and since then NCD has been collecting data on more than 95% of all surgical operations across Japan in collaboration with the clinical societies. NCD is also connected with the participating societies’ board of certification systems, which makes it unique among other large-scale clinical registries in the world. Today, more than 5,400 hospitals and clinics are participating in NCD with the accumulated data of 20 million cases (approximately 2 million each year).

HQA has developed risk models for different groups of surgical procedures that help us develop several practical tools aimed for medical professionals in the joint research activity with Japan Cardiovascular Surgery Database (JCVSD). One of those tools is JapanSCORE, which allows users to calculate a patient’s post-operative risk of mortality and morbidities. Another tool called RiskCalculator returns a medical professional the calculated risk of mortality and morbidity in a real-time manner after s/he inputs a minimum number of pre-operative risk information. Both tools can be used in medical team meetings as well as in sessions with patients to reach better informed consent. Just like JCVSD’s JapanSCORE and RiskCalculator, feedback tools based on the NCD data have been provided to different subspecialty surgical areas including the gastroenterological surgery and thoracic surgery. All of these activities help Japan’s healthcare quality initiatives in various places, and HQA is proud take part in it.

Since 2014, HQA has been participating in the post marketing surveillance studies based on NCD, in collaboration with PMDA (Pharmaceuticals and Medical Devices Agency), Academic societies and

device manufacturers. Also, starting in 2017, HQA has led a new initiative at NCD of collecting diagnosis procedure combination data and insurance claims data from participating facilities. Data on the use of medical products as well as on billings from these data are being used to supplement the clinical information collected in the registries for conducting clinical and health services research.

Future Directions

Clinical databases like NCD are the core components of quality improvement initiatives across the multiple subspecialties. HQA supports NCD’s systematic data collection, data management, practical analyses, and the development of useful feedback systems. Recently, non-surgical fields such as clinical oncology are also joining NCD and this trend has become stronger. Our benchmarking projects backed up by NCD’s big data will keep driving the quality improvement activities in many healthcare fields.

Increasing numbers of clinical research output has been coming out of the detailed analyses on NCD data in collaboration with each specialty field. Besides professional societies, medical device firms have started the operation of their post-marketing surveillance studies in collaboration with NCD. Working with NCD, the industry, PMDA, and the related medical societies, HQA helps the project move forward through academic support. Furthermore, HQA has been involved in international collaborative research work with database activities such as American College of Surgeon’s NSQIP and Asian Cardiac Database while contributing to the quality improvement activities in different regions of the world.

Publications

1. Kumamaru H, Kakeji Y, Fushimi K, Ishikawa KB, Yamamoto H, Hashimoto H, Ono M, Iwanaka T, Marubashi S, Gotoh M, Seto Y, Kitagawa Y, Miyata H. Cost of postoperative complications of lower anterior resection for rectal cancer: a nationwide registry study of 15,187 patients. *Surg Today*. 2022; 52 (12): 1766–74.

2. Shoji S, Kohsaka S, Kumamaru H, Yamaji K, Nishimura S, Ishii H, Amano T, Fushimi K, Miyata H, Ikari Y. Cost reduction associated with transradial access in percutaneous coronary intervention: A report from a Japanese nationwide registry. *Lancet Reg Heal - West Pacific*. 2022; 28: 100555.
3. Higuchi R, Kumamaru H, Kohsaka S, Saji M, Takamisawa I, Nanasato M, Shimokawa T, Shimizu H, Takayama M. Outcome of Nonagenarians Undergoing Transfemoral Transcatheter Aortic Valve Replacement: A Nationwide Registry Analysis From Japan. *JACC Asia*. 2022; 2 (7): 856–64.
4. Hoshino N, Endo H, Hida K, Kumamaru H, Hasegawa H, Ishigame T, Kitagawa Y, Kakeji Y, Miyata H, Sakai Y. Laparoscopic Surgery for Acute Diffuse Peritonitis Due to Gastrointestinal Perforation: A Nationwide Epidemiologic Study Using the National Clinical Database. *Ann Gastroenterol Surg*. 2021; 6 (3): 430–44.
5. Ichinose J, Yamamoto H, Aokage K, Kondo H, Sato Y, Suzuki K, Chida M. Real-world perioperative outcomes of segmentectomy versus lobectomy for early-stage lung cancer: a propensity score-matched analysis. *Eur J cardio-thoracic Surg Off J Eur Assoc Cardio-thoracic Surg*. 2022; 63 (1).
6. Kaibori M, Ichihara N, Miyata H, Kakeji Y, Nanashima A, Kitagawa Y, Yamaue H, Yamamoto M, Endo I. Surgical outcomes of laparoscopic versus open repeat liver resection for liver cancers: A report from a nationwide surgical database in Japan. *J Hepatobiliary Pancreat Sci*. 2022; 29 (8): 833–42.
7. Kofunato Y, Takahashi A, Gotoh M, Kakeji Y, Seto Y, Konno H, Kumamaru H, Miyata H, Marubashi S. Geriatric Risk Prediction Models for Major Gastroenterological Surgery Using the National Clinical Database in Japan: A Multicenter Prospective Cohort Study. *Ann Surg*. 2020; 275 (6): 1112–20.
8. Kono E, Isozumi U, Nomura S, Okoshi K, Yamamoto H, Miyata H, Yasufuku I, Maeda H, Sakamoto J, Uchiyama K, Kakeji Y, Yoshida K, Kitagawa Y. Surgical Experience Disparity Between Male and Female Surgeons in Japan. *JAMA Surg*. 2022; 157 (9): e222938.
9. Okamura A, Yamamoto H, Watanabe M, Miyata H, Kanaji S, Kamiya K, Kakeji Y, Doki Y, Kitagawa Y. Association Between Preoperative HbA1c Levels and Complications after Esophagectomy: Analysis of 15,801 Esophagectomies From the National Clinical Database in Japan. *Ann Surg*. 2022; 276 (5): e393–9.
10. Nishimura S, Kumamaru H, Shoji S, Nakatani E, Yamamoto H, Ichihara N, Miyachi Y, Sandhu AT, Heidenreich PA, Yamauchi K, Watanabe M, Miyata H, Kohsaka S. Assessment of coding-based frailty algorithms for long-term outcome prediction among older people in community settings: A cohort study from the Shizuoka Kokuho Database. *Age and Ageing*. 2020; 51(3): 1–9.
11. Ikeda N, Yamamoto H, Taketomi A, Hibi T, Ono M, Niikura N, Sugitani I, Isozumi U, Miyata H, Nagano H, Unno M, Kitagawa Y, Mori M. The impact of COVID-19 on surgical procedures in Japan: analysis of data from the National Clinical Database. *Surg Today*. 2022; 52 (1): 22–35.
12. Sato Y, Yamamoto H, Ikeda N, Konishi H, Endo S, Okada Y, Kondo H, Shintani Y, Toyooka S, Nakamura H, Hoshikawa Y, Chen-Yoshikawa TF, Yoshino I, Kakizoe T, Chida M. The impact of COVID-19 on thoracic surgical procedures in Japan: Analysis of data from the National Clinical Database. *Lung Cancer*. 2022; 172: 127–35.
13. Okoshi K, Endo H, Nomura S, Kono E, Fujita Y, Yasufuku I, Hida K, Yamamoto H, Miyata H, Yoshida K, Kakeji Y, Kitagawa Y. Comparison of short term surgical outcomes of male and female gastrointestinal surgeons in Japan: retrospective cohort study. *BMJ*. 2022; 378: e070568.

Laboratory for Cryo-Electron Microscopy

Project Associate Professor

Chieko Saito, Ph.D.

Project Assistant Professor

Fabian Eisenstein, Ph.D.

Homepage

Introduction and Organization

The Laboratory of Cryo-Electron Microscopy was established in April 2022 to promote the analysis of biological specimens using cryo-electron microscopy in cooperation with JEOL Ltd. The duration of the laboratory is four years (April 1, 2022 - March 31, 2026).

This laboratory aims to promote the use of cryo-electron microscopy in society and to advance cryo-electron microscopy as a research platform, and to foster human resources who will play a role in this effort. We will conduct research on sample preparation methods, high-speed imaging methods, and three-dimensional structural analysis methods to obtain high-resolution images for single-particle analysis and tomographic analysis. In addition, by providing educational support for lectures on the principles of cryo-electron microscopy and practical training, sample preparation, and three-dimensional structural analysis methods, we aim to develop human resources capable of promoting structural analysis of biological specimens through cryo-electron microscopy.

The current members of the laboratory for Cryo-Electron Microscopy are: Project Associate Professor (Chieko Saito, appointed in November 2022), Project Assistant Professor (Fabian Eisenstein, appointed in January 2023 – March 2024), and Technical Assistant (Toshie Furuya, appointed in August 2022).

Clinical activities

No special note.

Teaching activities

To solve the technical issues for cryo-electron microscopy to applying life science research and drug discovery, we have worked to cultivate human resources such as graduate students and young researchers through joint research.

In FY2023, we helped plan and implement a cryo-electron microscopy technology workshop held jointly with the Laboratory of Structural Biology (Kikkawa-lab), the Laboratory of Advanced Structural Studies (Danev-lab), the Institute for Quantitative Bioscience (Kurumizaka-lab), and laboratories from the Graduate School of Science (Nureki-lab). In addition, we accepted students from the World-leading Graduate School of Life Science and Technology (WINGS-LST) program into the above-mentioned training course and conducted the training as a practical training session. From October 2023, we held a monthly meeting regarding cryo-FIB-SEM/tomography to promote network formation and information sharing. We participated in the open campus event at the University of Tokyo Kashiwa Campus, and conducted a tour of the cryo-electron microscope and provided explanations using posters at the Industry-Academia-Government-Public Collaboration Building at Kashiwa Campus 2.

Research activities

By actively applying cryo-electron microscopy to industry-academia collaborative research, we aim to contribute to solving various issues in industry. In addition, we will also conduct state-of-the-art room-temperature electron microscopy (Volume EM) to complement cryo-electron microscopy analysis.

The following joint research was conducted in FY 2023. Department of Molecular Biology, Graduate School of Medicine, The University of Tokyo (Mizushima-Lab), WINGS-LST program students (Graduate School of Engineering, Hirabayashi-Lab), The University of Tokyo Hospital (Cardiovascular Medicine, Dr. Tsushima), Institute of Multi-disciplinary Research for Advanced Materials, Tohoku University (Mizukami-Lab), Department of Applied Chemistry, Graduate School of Engineering, The University of Tokyo (Aida-lab, Dr. Miki), Institute for Interdisciplinary Research, Okayama University (Senju-Lab), etc.

We provided consulting and management services for the provision of support using the cryo-electron microscope shared facility in the Faculty of Medicine Experimental Research Building, which is operated with the support of the Japan Agency for Medical Research and Development's Basis for Supporting Innovative Drug Discovery and Life Science Research (AMED BINDS Phase2, second phase to begin in April 2023). We also managed the two cryo-electron microscopes installed at the Kashiwa 2 Campus (CRYO ARM300 II (JEM-3300, JEOL Ltd.) and CRYO ARM200 (JEM-Z200, JEOL Ltd.)). We cooperated in the performance evaluation of the room-temperature focused ion beam processing and observation device (JIB-PS500i, JEOL Ltd.) and began joint research involving the free loan of the equipment.

References

1. Zhang, W., Nishimura, T., Gahlot, D., **Saito, C.**, Davis, C., Jefferies, H. B. J., Schreiber, A., Thukral, L. & Tooze, S. A. Autophagosome membrane expansion is mediated by the N-terminus and cis-membrane association of human ATG8s. *eLife* **12**, (2023).
2. Shimizu, T., Tamura, N., Nishimura, T., **Saito, C.**, Yamamoto, H. & Mizushima, N. Comprehensive analysis of autophagic functions of WIPI family proteins and their implications for the pathogenesis of β -propeller associated neurodegeneration. *Hum. Mol. Genet.* **32**, 2623–2637 (2023).

Department of Cellular and Tissue Communications

Project Professor

Jun K. YAMASHITA, M.D.,Ph.D.

Project Assistant Professor

Tomohiro Minakawa, Ph.D.

※The following information is the same as that of the previous year for certain reasons.

Homepage <https://www.m.u-tokyo.ac.jp/english/departments/units.html>

Introduction and Organization

The Department of Cellular and Tissue Communications was established on July 1, 2022, with Takara Bio Inc. as the investor and the Department of Cardiac Surgery (Prof. Minoru Ono) as the collaborating department. The main purpose of this department is to elucidate new actions and roles of extracellular vesicles (EVs) in diseases, which have been recently highlighted as a new type of intercellular communication, and to develop new next-generation therapies using EVs. One Project Professor and one Project assistant professor have been appointed, and Dr. Yamashita and Dr. Minagawa have been appointed to these positions respectively.

The details of the reason for the establishment, significance, and research content are as follows.

The purpose of this department is to develop research on novel cellular and tissue communications focusing on a new biological phenomenon called “phenotypic synchronization of cells (PSyC)” via extracellular vesicles (EVs), which has recently been discovered and reported in Japan, to elucidate new pathological conditions and to develop new therapeutic methods using EVs. EVs are considered to be involved in various biological phenomena and pathological conditions by delivering various molecules in various forms, and are an important new research target in medical biology. Entering this research field based on the world's first discovery of the unique function of

EVs (PSyC) would contribute to the University for securing its leading position in EV research and EV treatment. The establishment of this department will benefit for academic, research, and social activities.

The focus of this course is to explore the possibility of pathological analysis and therapeutic application based on basic research on the PSyC phenomenon. We also aim to develop human resources who will pioneer and develop new research areas based on the research content of this course.

[Research Contents]

1) Phenotypic Synchronization of Cells (PSyC): Using cells that can mark EVs, we would like to conducting real-time monitoring with high spatial-temporal resolution to elucidate the actual mode of EV exchange, the signaling molecules in EVs and their mechanisms of action.

(2) Significance of PSyC and EVs in pathological conditions: PSyC is considered to be involved not only in synchronization of differentiation, but also broadly in homeostasis, aging, and regeneration processes. The physiological and pathophysiological significance of PSyC will be clarified.

3) Therapeutic application of PSyC and EVs: Development of next-generation novel therapies utilizing cellular and tissue communications and PSyC with EVs. Explore the possibilities of anti-aging and rejuvenation therapies through cardiac regeneration, anti-atherosclerosis, and improvement of vascular function.

The following are assumed to be possible,

- EV is an area that has recently been highlighted and the research is progressing rapidly, but the "synchronization of cellular phenotypes" is a unique discovery that was reported for the first time. Furthermore, the new roles and significance of EVs will be clarified by analysis of the latest technologies such as real-time monitoring, opening up a new academic field centered on cellular and tissue communications.

- The analysis of pathological conditions from a different perspective, including communication with EVs, will lead to a new understanding of diseases and the development of new treatment methods.

- By being the first to launch EV therapies supported by scientific findings, we can lead the development of new EV therapies worldwide.

- The potential for the development of completely new therapies such as anti-aging and rejuvenation therapies can also be expected.

- The company can expect to commercialize EVs through its investors and develop the application of therapeutics and other industrialization.

The research targets of cellular and tissue communications and cell differentiation are related to stem cell biology and developmental biology. And those of heart failure, atherosclerosis, tissue aging, are related to cardiovascular medicine and surgery, which may be the initial therapeutic targets for heart and blood vessels. The research targets centered on EV-mediated PSyC are highly unique, but the results can be linked to various related fields and have high potential for development. Thus, this course is a new research field that has not existed at the University of Tokyo before, and it can lead to new interactions, research linkages, and industry-academia collaborations.

Research activities

The following is an overview of our research to date. Drs. Yamashita and Minagawa, members of our faculty, discovered and reported the PSyC phenomenon (Minakawa, *J Extracell Vesicles*, 2021). Yamashita and colleagues have been conducting basic research on cardiovascular cell differentiation using pluripotent stem cells and its application to regenerative medicine

and other fields. With the differentiation of pluripotent stem cells into cardiovascular cells as the basis and core of their research, they have conducted a series of wide-ranging research activities, including basic research on various types of differentiation, induction of cardiovascular cells from human pluripotent stem cells, application of 3D organization to cardiac regeneration therapy and creation of new disease models, and commercialization of these products.

(1) Cardiovascular cell differentiation of pluripotent stem cells and application to regenerative medicine: We have conducted original and advanced research on cardiovascular cell differentiation and regeneration using pluripotent stem cells (ES cells and iPS cells). Using Flk1-positive cells as common progenitors in mouse ES cells, we have established a new experimental system that allows us to investigate the differentiation mechanism of cardiovascular cells systematically (*Nature*, 2000). We are the first to identify cardiac progenitor cells (FCV cells) that differentiate into cardiomyocytes at high rates (*FASEB J*, 2005) and to successfully differentiate iPS cells into cardiovascular cells (*Circulation*, 2008; Best Paper Award in the Basic Science category of the same journal). Based on these achievements, we have analyzed the vascular differentiation mechanism of stem cells (*Blood*, 2009; *J Cell Biol*, 2010; *Blood*, 2011 (front cover); *Stem Cells*, 2012a), developed cell therapy using cardiac tissue sheets (*Stem Cells*, 2012b). We have developed novel methods for induction of cardiac/endothelial cell differentiation and purification of human iPS cells (*PLoS One*, 2011a, 2011b, 2017, 2020), and technologies for cardiac tissue formation from iPS cells, including simple multiple layering of cell sheets using gelatin hydrogel (*Sci Rep*, 2014, 2015, 2016). The application of these technologies to cardiac regenerative medicine is underway (in collaboration with the Department of Cardiac Surgery of University of Tokyo and Kyoto University, and iHeart Japan, Inc.)

(2) Development and application of novel pathological models: We developed the world's first model for a lethal arrhythmia, Torsade de Pointes (TdP), using iPS cell-derived mini 3D tissue (Kawatou, *Nat Commun*, 2017). The model will be further developed for application to drug safety studies and in vitro disease reproduction and therapeutic research.

(3) Pioneering new EV biology & medicine: The

discovery of EV-induced cellular phenotypic synchronization (Minakawa, J Extracell Vesicles, 2021) will bring a new research field to the EV world. EVs, together with real-time monitoring, will elucidate a variety of new functions of EVs. We will also investigate the application of EVs to novel cardiac regeneration therapies based on their currently discovered ability to induce myocardial differentiation.

(4) Regeneration of human hearts: We would like to making it possible to regenerate human hearts by enabling the proliferation of human cardiomyocytes and the conversion of cardiac progenitor cells into stem cells. We are currently analyzing the regulatory mechanism of human cardiomyocyte proliferation using various bioinformatics methods and our university's supercomputer.

(5) AMPK-based anti-aging and rejuvenation strategies: Metformin, an AMPK activator, is a potential longevity drug that can extend lifespan, and undifferentiated transcription factors used to induce iPS cells have also been suggested to have lifespan-extending effects. AMPK activation, which serves as a link between these factors, has been shown to induce naïve conversion of pluripotent stem cells (Liu, iScience, 2021). A similar mechanism has been found to operate in human cells (Yang, BioRxiv, 2022).

(6) Applications of Bioinformatics to pluripotent stem cells. Development of a new cytotoxicity detection system: We are developing a new cytotoxicity detection system using the pluripotent stem cells with their broad gene expression potential due to their pluripotency and low genomic modification (Yamane, iScience, 2022; Mori, BMC Bioinformatics, 2023). (in collaboration with Dr. Wataru Fujibuchi).

With these studies as a background, we have been working mainly on (3), (4), (5), and (6) since our appointment in FY2022.

References

[Papers]

1. Yamane J, Wada T, Otsuki H, Inomata K, Suzuki M, Hisaki T, Sekine S, Kouzuki H, Kobayashi K, Sone H, Yamashita JK, Osawa M, Saito MK, Fujibuchi W. StemPanTox: A fast and wide-target drug assessment system for tailor-made safety evaluations using personalized iPS cells. iScience. 6;25:104538, 2022.
2. 大塚 悟史、中尾 洋一: 春ウコンに含まれるアストロサイト分化誘導促進物質の同定, 化学と生物, 61:6-8, 2023

[Awards]

皆川朋皓, 第 28 回 (令和 4 年度) 日本炎症・再生医学会奨励賞 2022.7.7

[Lectures]

1. 山下潤. 幹細胞と組織工学による組織機能の構成的再現. 第 43 回日本炎症再生医学会シンポジウム, 2022.7.6.
2. 皆川朋皓, 山下潤. 近接する細胞へのエクソソーム・細胞外小胞送達による細胞形質同調. 第 43 回 日本炎症・再生医学会, 2022.7.7
3. 山下潤. 細胞外小胞の新しい機能と可能性ー細胞形質を制御するー. 第 81 回日本癌学会学術集会・共催セミナー, 2022.9.30.
4. Yamashita JK. Cardiovascular regeneration with human iPS cell-derived heart tissue. Symposium on Medical Exchange of Shanghai University and the University of Tokyo, 2022.11.17.
5. Kawatou M, Minatoya K, Ashihara T, Yamashita JK. Human iPS cell-engineered heart tissue to reproduce ventricular fibrillation in vitro. 第 87 回日本循環器学会学術集会, 2023.3.11.
6. 山下潤. 再生医療への幹細胞/ティッシュエンジニアリング融合技術の役割と新展開. 第 22 回日本再生医療学会総会シンポジウム, 2023.3.24.
7. 山下潤. 血管内塞栓を形成しない安全な基材による新しい効率的な筋前駆細胞移植法の開発. 第 22 回日本再生医療学会総会, 2023.3.25.
8. 皆川朋皓, 山下潤. 隣接細胞間における小胞動態のライブイメージング. 生物物理学会中部支部講演会, 2023.3.31.

Department of Next-Generation Endoscopic Computer Vision

Project Associate Professor

Yosuke Tsuji, M.D., Ph.D.

Project Research Associate

Hiroya Mizutani, M.D., Ph.D., Tomonori Aoki, M.D., Ph.D.

※The following information is the same as that of the previous year for certain reasons.

Introduction and Organization

This Social Cooperative Chair was launched in January 2023 with the investment of AI Medical Services, Inc. As an affiliated chair of the University of Tokyo Graduate School of Medicine, it is also supported by the Department of Gastroenterology (Prof. Mitsuhiro Fujishiro).

The main research project of the department is the use of AI in gastrointestinal endoscopy. As a result of the introduction of the option of endoscopy in population-based gastric cancer screening (a public medical service aiming at reducing mortality from gastric cancer) from 2016, the number of endoscopic examinations has dramatically increased, and the increased workload on physicians and the risk of missing gastric cancer have become major issues. At the same time, since endoscopy is an examination method that depends on the skill of the physician, the difference in skill is also an issue. Recently, many attempts to apply the latest AI technologies such as Deep Learning to the medical field have been reported, and there are high expectations for the application of AI in the field of endoscopy. The purpose of our department is to conduct research and development for the utilization of AI in endoscopy and evaluate the results in clinical practice.

Clinical activities

Our department is not directly involved in the clinical practice. Dr. Tsuji (Project Associate Professor) is the head of the Gastrointestinal Tract Group in the

Department of Gastroenterology at the University of Tokyo Hospital, where he manages the treatment of the gastrointestinal tract. Together with Drs. Hiroya Mizutani, and Tomonori Aoki (Project Research Associate), who also belong to the Gastrointestinal Tract Group of the Department of Gastroenterology at the University of Tokyo Hospital, he is involved in many diagnoses and treatments using gastrointestinal endoscopy.

Teaching activities

Our department is not directly involved in education. Dr. Tsuji (Project Associate Professor) is in charge of a lecture on "Non-neoplastic Bowel Disease" in the organized course "Gastroenterology" for the second-year medical students in the Department of Internal Medicine, School of Medicine, the University of Tokyo.

Research activities

Our department will conduct research, development, and clinical evaluation of software programs that assist physicians in diagnosis using the latest image analysis technology. Specifically, the following two points will be the main focus of the research:

- (1) We will develop AI equipped with endoscopists' knowledge to improve the quality of endoscopic diagnosis by equalizing the endoscopic diagnosis and reducing missed diagnoses.
- (2) To establish next-generation endoscopic diagnosis

and treatment methods using AI, we will acquire, process, and classify data based on actual clinical experience. We will resolve issues related to the small number of data on rare cases, annotation cost, etc., which are challenges in the social implementation of endoscopic AI, from the perspective of image analysis technology.

To develop an endoscopic diagnosis support AI, a large amount of high-quality "training data," i.e., a large number of high-quality endoscopic images and videos of diseases, is first required. In addition, information such as the location of the disease, the extent of the disease, and the final diagnosis must be linked to the image data. For this reason, we are building a system for training AI by accumulating a large number of endoscopic images as high-quality video data in collaboration with the University of Tokyo and other facilities. After accumulating a certain number of data, we will develop an AI to support disease detection and differential diagnosis and conduct necessary trials to verify the effectiveness of the AI and to introduce it into actual clinical practice in the future.

gastric cancer. *J Gastroenterol.* 2022 Dec;57(12):952-961

References

1. Nagao S, Tani Y, Shibata J, Tsuji Y, Tada T, Ishihara R, Fujishiro M. Implementation of artificial intelligence in upper gastrointestinal endoscopy. *DEN Open.* 2022 Mar 15;2(1):e72.
2. Ochiai K, Tada T, Shibata J, Nagao S, Tsuji Y, Fujishiro M, Ishihara S. Artificial Intelligence in Colonoscopy: Exploring Computer-aided Detection Systems Stomach and Intestine 2022, 57(10) :1298-1304
3. Kubota D, Tsuji Y, Mizutani H, Nagao S, Fujishiro M. An unexpected adverse event of endoscopic ultrasonography: acute aortic dissection. *Gastrointest Endosc.* 2022 Nov;96(5):866-867.
4. Hisada H, Tsuji Y, Obata M, Cho R, Nagao S, Miura Y, Mizutani H, Ohki D, Yakabi S, Takahashi Y, Sakaguchi Y, Kakushima N, Yamamichi N, Fujishiro M. The impact of sarcopenia on short- and long-term outcomes of endoscopic submucosal dissection for early

Next-Generation Precision Medicine Development Laboratory

Project Associate Professor

Kousuke Watanabe, M.D., Ph.D.

Project Lecturer

Akiko Kunita, Ph.D.

Project Research Associate

Miho Ogawa, M.D., Ph.D.

Introduction and Organization

In June 2019, The University of Tokyo, National Cancer Center Japan, and Konica Minolta, Inc. agreed to develop Todai OncoPanel (TOP), a next-generation comprehensive cancer genomic panel (CGP). TOP was initially developed by Professor Aburatani, The University Tokyo Research Center for Advanced Science and Technology and Hiroyuki Mano, former professor at The University of Tokyo and current Director of National Cancer Center Research Institute, Japan. The research collaboration combines the knowledge of Ambry Genetics Corporation, a Konica Minolta company, and its global gene diagnostic technology, with the TOP technology to reinforce the informatics foundation technology of the TOP and develop a next-generation CGP. The Department of Next-Generation Precision Medicine Development Laboratory was established in April 2021 as a Social Collaboration Department within 22nd Century Medical and Research Center of The University of Tokyo Hospital, collaborating with Konica Minolta, Inc.

Clinical activities

As a Social Collaboration Department within 22nd Century Medical and Research Center, we do not

directly engage in clinical activities. Dr. Watanabe is involved in cancer genomic medicine at The University of Tokyo Hospital through oversight of the Expert Panel. GenMineTOP was included in the national health insurance coverage as a CGP test in August 2023.

Teaching activities

As a Social Collaboration Department within 22nd Century Medical and Research Center, we do not directly engage in teaching activities. When M4 medical students came to the Department of Clinical Genomics for a one-month rotation in fiscal year 2023, former Project Associate Professor Dr. Kage, gave lectures and participated in Expert Panels with the students.

Research activities

TOP can detect a large number of gene mutations with its DNA panel and gene fusions with its RNA panel. At the Department of Next-Generation Precision Medicine Development Laboratory, we focus on (1) optimization of pathological specimens for CGP tests, (2) analysis TOP quality metrics, and (3) analysis of non-small cell lung cancer using TOP. We are conducting research aimed at improving the performance of GenMineTOP, which has been included in insurance coverage.

(1) Best tissue processing practices for CGP tests with RNA panel

Background: Formalin-fixed, paraffin-embedded (FFPE) samples are valuable resources routinely used for pathology and clinical CGP tests. However, they also represent a multistage process that is not standardized, especially for RNA sequencing. Therefore, we evaluated the impact of storage time and temperature on DNA and RNA integrity in human FFPE specimens.

Methods: Unstained sections from 20 FFPE specimens from 2018-2021 were stored at various temperatures for different durations, including room temperature (20-22 °C) and lower temperatures ranging from 4 °C to -30 °C and -80 °C. DNA/RNA was extracted from each 10 mm section using spin columns. The effect of storage time on the yield and quality of both DNA and RNA was evaluated using fluorescence spectrometry, fragment size distribution, and qPCR.

Results: DNA/RNA yield did not change after one year of storage at room temperature. However, the quality of DNA/RNA decreased over time. Storage at 4°C or below prevented degradation of nucleic acid quality. The quality of both DNA/RNA from FFPE blocks stored for more than 1 year deteriorated more than that of FFPE samples stored for less than 1 year. RNA showed a more pronounced age-related degradation than DNA.

Conclusions: FFPE specimens prepared within 1 year are suitable and it is recommended to section immediately prior to CGP testing (within 1 month). DNA/RNA quality has been maintained for 1 year by storing unstained sections at 4 °C or below.

(2) Analysis of TOP quality metrics

Background: The quality of nucleic acids extracted from FFPE specimens varies between samples. This study aims to clarify how nucleic acid quality impacts sequencing quality and to identify differences in nucleic acid quality among hospitals and cancer types.

Methods: A total of 585 samples analyzed using TOP through AMED research or advanced medical care were evaluated. Three nucleic acid quality metrics (ddCq, Q-value, DV200) and five sequencing quality metrics (on-target rate, average depth, coverage uniformity, target exon coverage, housekeeping gene coverage) were assessed.

Results: For the DNA panel, ddCq was a predictor of

average depth, and the Q-value was a predictor of coverage uniformity. To achieve optimal results, both ddCq and Q-values needed to be high. For the RNA panel, DV200 was found to be a useful indicator for housekeeping gene coverage. Significant differences in DNA quality (ddCq and Q-values) were observed among hospitals. Differences between cancer types were also identified: Q-values were lowest in lung cancer and highest in cervical cancer, while DV200 was highest in lung cancer and lowest in colorectal cancer. **Conclusions:** The metrics ddCq, Q-value, and DV200 each exhibited unique characteristics and were associated with sequencing quality. Variations in nucleic acid quality were observed not only between cancer types but also across specimen collection facilities. Further research on pre-analytical processes is warranted.

(3) Analysis of non-small cell lung cancer using TOP

Background: In non-small cell lung cancer (NSCLC), numerous therapeutic targets, including genetic mutations, gene fusions, and exon skipping, have been identified. The DNA and RNA twin-panel system TOP is expected to efficiently detect therapeutic targets.

Methods: Sixty NSCLC samples analyzed using TOP through AMED research or advanced medical care were evaluated. Data from other gene panel tests (DNA panels) conducted as part of insurance-covered medical care were downloaded from the C-CAT database and compared with the TOP analysis results.

Results: In adenocarcinoma, EGFR mutations were identified in 17 cases (33%), and ERBB2 mutations were found in 6 cases (12%). Pathogenic germline mutations in BRCA1 and BRCA2 were each detected in one case. The RNA panel detected 11 gene fusions, all of which were in adenocarcinoma. Specifically, one case each of EML4-ALK and KIF5B-RET fusions was identified, while the remaining nine cases involved novel fusions with unknown pathogenicity. Additionally, MET exon 14 skipping was confirmed in 4 out of 60 NSCLC samples (7%), which was statistically significantly higher than the frequency observed in the C-CAT database (37/1514).

Conclusions: TOP detected therapeutic targets in NSCLC. The RNA panel demonstrated a potential for highly sensitive detection of MET exon 14 skipping.

Publications

1. Matsumoto Y, Kage H, Morota M, Zokumasu K, Ando T, Maemura K, Watanabe K, Kawakami M, Hinata M, Ushiku T, Nakajima J, Nagase T. Integrin alpha 2 is associated with tumor progression and postoperative recurrence in non-small cell lung cancer. *Jpn J Clin Oncol*. 2023 Jan 6;53(1):63-73. PMID: 36151049
2. Kage H, Shinozaki-Ushiku A, Ishigaki K, Sato Y, Tanabe M, Tanaka S, Tanikawa M, Watanabe K, Kato S, Akagi K, Uchino K, Mitani K, Takahashi S, Miura Y, Ikeda S, Kojima Y, Watanabe K, Mochizuki H, Yamaguchi H, Kawazoe Y, Kashiwabara K, Kohsaka S, Tatsuno K, Ushiku T, Ohe K, Yatomi Y, Seto Y, Aburatani H, Mano H, Miyagawa K, Oda K. Clinical utility of Todai OncoPanel in the setting of approved comprehensive cancer genomic profiling tests in Japan. *Cancer Sci*. 2023 Apr;114(4):1710-1717. PMID: 36601953
3. Kage H, Oda K, Muto M, Tsuchihara K, Okita N, Okuma Y, Kikuchi J, Shirota H, Hayashi H, Kokuryo T, Sakai D, Hirasawa A, Kubo M, Kenmotsu H, Akiyama N, Shinozaki-Ushiku A, Tanabe M, Ushiku T, Miyagawa K, Seto Y. Human resources for administrative work to carry out a comprehensive genomic profiling test in Japan. *Cancer Sci*. 2023 Jul;114(7):3041-3049. PMID: 37165760
4. Ohara K, Miyawaki S, Nakatomi H, Okano A, Teranishi Y, Shinya Y, Ishigami D, Hongo H, Takayanagi S, Tanaka S, Shinozaki-Ushiku A, Kohsaka S, Kage H, Oda K, Miyagawa K, Aburatani H, Mano H, Tatsuno K, Saito N. Case report and literature review: exploration of molecular therapeutic targets in recurrent malignant meningioma through comprehensive genetic analysis with Todai OncoPanel. *Front Neurol*. 2023 Nov 23;14:1270046. PMID: 38073632
5. Xi Q, Kage H, Ogawa M, Matsunaga A, Nishijima A, Sone K, Kawana K, Oda K. Genomic Landscape of Endometrial, Ovarian, and Cervical Cancers in Japan from the Database in the Center for Cancer Genomics and Advanced Therapeutics. *Cancers (Basel)*. 2023;27;16(1):136. PMID: 38201563
6. Kondo A, Shinozaki-Ushiku A, Rokutan H, Kunita A, Ikemura M, Yamashita H, Seto Y, Nagae G, Tatsuno K, Aburatani H, Koinuma D, Ushiku T: Loss of Viral Genome with Altered Immune Microenvironment During Tumour Progression of Epstein-Barr Virus-Associated Gastric Carcinoma. *J Pathol*. 2023;260:124-36.PMID:36806225

Department of Tissue Stem Cells and Life Dentistry

Project Professor

Makoto Komura, M.D., Ph.D.

Project Lecturer

Yukiyo Asawa, D.V.M., Ph.D.

※The following information is the same as that of the previous year for certain reasons.

Homepage <http://plaza.umin.ac.jp/~tsc-lds/manage.html>

Introduction and Organization

A social cooperation course, The Department of Tissue Stem Cells and Life Dentistry was a collaborative department established in the department of tissue engineering, the University of Tokyo Hospital on November 19, 2018.

The research is currently based in University of Tokyo Hospital Tissue Engineering Department, Department of Oral and Maxillofacial Surgery, and Department of Pediatric Surgery.

The goal of our department is to succeed in translational research, from basic to clinical with the promotion of technology development on tissue organ regeneration, funded by Sheep Medical Co., Ltd. (formerly Dental Assist Co., Ltd.).

Major research projects include: research to elucidate self-renewal mechanisms using template-encapsulated tissue bodies (bio sheet/ bio tube) for trachea, gingiva and cornea regeneration, development of pulp stem cell culture methods, research on humoral factors in dental pulp culture supernatant fluid, establishment of techniques to induce bone differentiation in human umbilical cord, and analysis of oral microflora.

In 2022, the department is currently headed by a Project Professor, was assisted by a Project Lecturer.

Teaching activities

We shared the appeal of basic research to undergraduates through laboratory tours.

With the cooperation of Department of Pediatric Surgery, we are preparing to give lectures to master and Ph.D. students. On January 17, 2023, We gave a lecture on "Pediatric Surgery and Regenerative Medicine" in the Department of Reproductive, Developmental and Aging Sciences.

We also gave research guidance to master and Ph.D. students majoring in pediatric surgery and oral and maxillofacial surgery through practical training and exercises.

Research activities

In our study, we use somatic stem cell that exists in bio tissue, and we try to stimulate the somatic cell. By using dental pulp-derived stem cell, cartilage stem cell, and umbilical cord-derived stem cell, we are working to make up for the functional and structural defects. The target organs for this specific reproductions are, bone, cartilage, skin and muscle (including gingiva).

The following are the research topics of our department in 2020:

- Self-regeneration mechanism identification of skin mold encapsulation tissue
 - Structure analysis of skin-encapsulated tissue

- Construction of regeneration model using skin-encapsulated tissue
- Factor examination of regeneration model
- Development of dental pulp stem cell culture method
 - Development of human dental pulp stem cell culture method
 - Analysis on human dental pulp cell
 - Development of mouse dental pulp stem cell culture method
 - Analysis on mouse dental pulp cell
 - Evaluation of mouse dental pulp cell differentiation
- Proliferation of cartilage stem cell
 - Construction of tracheal cartilage anastomosis site evaluation model
 - Technical development of strengthened tracheal anastomosis site
 - Dynamic measurement of tracheal anastomosis site
 - Functional evaluation of human ES cell
- Bone differentiation culture technique of human umbilical cord
 - Development of umbilical cord cell culture method while maintaining undifferentiated form
 - Development of bone differentiation induction method
- Analysis of oral microflora
 - Identification of bacteria with anti-inflammatory properties.
Anti-inflammatory action of bacteria against periodontopathic bacteria.

References

- 1: Shimizu R, Asawa Y, Komura M, Hoshi K, Hikita A. Superior stemness of a rapidly growing subgroup of isolated human auricular chondrocytes and the potential for use in cartilage regenerative therapy. *Regen Ther.* 2022 Jan 4;19: 47-57.
- 2: Yokote F, Yamauchi Y, Komura H, Tanuma T, Sakao Y, Kawamura M, Komura M. A novel method of tracheal anastomosis healing using a single submucosal injection of basic fibroblast growth factor: initial report. *Eur J Cardiothorac Surg.* 2022 Mar 24;61(4):917-924.

Conference Presentations

- 1: The 21st Annual Meeting of the Japanese Society for Regenerative Medicine. SP-13-2 March 17, 2022. Asawa, Y., Shiraishi, K., Nishida, T., Komura, H., Kumagai, K., Seto, I., Abe, T., Hikita, A., Komura, M., Hoshi, K. Evaluation of cellular characteristics and bone differentiation potential of dental pulp cells derived from human permanent and wisdom teeth.
- 2: The 21st Annual Meeting of the Japanese Society for Regenerative Medicine. SP-19-6 March 19, 2022. Komura, H., Suzuki, K., Asawa, Y., Kanazawa, S., Shiraishi, K., Nakayama, Y., Komura, M. Skin regeneration by subcutaneously implanted periapical encapsulated tissue body (bio sheet).
- 3: The 76th Annual Meeting of the Japanese Society of Oral Medicine. April 21-23, 2022. Harada, T., Shiraishi, K., Asawa, Y., Abe, T., Komura, M., Hoshi, K. Basic study on mouse dental pulp cells for the development of bone regeneration technology.
- 4: The 76th Annual Meeting of the Japanese Society of Oral Medicine. April 21-23, 2022. Shiraishi, K., Harada, T., Kawakami, H., Kumagai, K., Abe, M., Asawa, Y., Komura, M., Hoshi, K. Characterization of dental pulp cells derived from human permanent teeth and evaluation of bone differentiation potential for development of bone regeneration therapy.

Department of Digital Mental Health

Project Professor

Norito Kawakami, M.D., Ph.D.

Project Associate Professor

Kotaro Imamura, Ph.D.

Project Lecturer

Asuka Sakuraya, Ph.D.

※The following information is the same as that of the previous year for certain reasons.

Homepage <https://dmh.m.u-tokyo.ac.jp/>

Introduction and Organization

The Department of Digital Mental Health was established in June 2022 as a social cooperation program in collaboration with the Graduate School of Medicine, The University of Tokyo and 15 companies. We conduct basic and applied research on digital mental health (DMH) technology and services, such as measuring mental health and developing intervention programs to maintain and promote mental health. We contribute to society by disseminating research findings for mental health and also contribute to medical education based on these findings. We mainly research how to apply digital health technology to mental health promotion in the workplace and health and productivity management systems. The Department of Digital Mental Health is the world's first department established in a university to apply DMH technology in the occupational mental health field. From our activity, the following results will be expected;

- 1) Innovative digital mental health solutions applying artificial intelligence (AI) and simulation models will be developed and widely disseminated to individuals, companies, and organizations to promote people's mental health.
- 2) Scientific evidence about the accuracy of measurement methods and effectiveness of

intervention programs will be accumulated, and evidence-based services applying DMH technologies will be established.

- 3) Strategies for the dissemination and implementation of evidence-based DMH services will be developed, and a framework for their quality assurance will be proposed to society.

Research activities

Mental health is an important issue for individuals, companies, organizations, and society. In particular, mental health became a major public health challenge during the COVID-19 pandemic. In the post-pandemic society, it will be important to develop DMH technology to support mental health in the workplace and community using digital tools. The main research topics are as follows:

- 1) Applying digital technologies such as AI and simulation models to promote DMH, and developing a fully automated and tailored stress management program guided by AI.
- 2) Evaluating the effectiveness of evidence-based DMH measurement and intervention programs using gold-standard methodology such as randomized controlled trials.
- 3) Developing effective strategies for the dissemination and implementation of evidence-

based DMH measurement and intervention programs to individuals, companies/organizations, and municipalities. We also research quality assurance frameworks for DMH services.

In addition to this, we will conduct extensive research on mental health in the digital society and "Society 5.0."

References

1. Fukasawa M, Umeda M, Akiyama T, Horikoshi N, Yasumura S, Yabe H, Suzuki Y, Bromet EJ, Kawakami N. Worry about Radiation and Its Risk Factors Five to Ten Years after the Fukushima Nuclear Power Plant Disaster. *Int J Environ Res Public Health*. 2022 Dec 16;19(24):16943. doi: 10.3390/ijerph192416943. PMID: 36554824; PMCID: PMC9778659.
2. Yasuma N, Shiozawa T, Ogawa M, Abe M, Igarashi M, Kawaguchi T, Sato S, Nishi D, Kawakami N, Yamaguchi S, Fujii C. What outcomes in community mental health research are important to caregivers of people with schizophrenia? An exploratory qualitative analysis of an online survey. *Neuropsychopharmacol Rep*. 2022 Dec;42(4):526-531. doi: 10.1002/npr2.12295. Epub 2022 Oct 10. PMID: 36217559; PMCID: PMC9773637.
3. Sasaki N, Akiyama H, Kawakami N, Nishi D. Preconception menstrual cycle disorder and antenatal depression: a cross-sectional study with prerecorded information. *J Psychosom Obstet Gynaecol*. 2022 Dec;43(4):411-418. doi: 10.1080/0167482X.2021.2010699. Epub 2021 Dec 9. PMID: 34882063.
4. Obikane E, Sasaki N, Imamura K, Nozawa K, Vedanthan R, Cuijpers P, Shimazu T, Kamada M, Kawakami N, Nishi D. Usefulness of Implementation Outcome Scales for Digital Mental Health (iOSDMH): Experiences from Six Randomized Controlled Trials. *Int J Environ Res Public Health*. 2022 Nov 27;19(23):15792.
5. Tsuji R, Nishi D, Sasaki N, Akiyama H, Kuroda R, Tsuno K, Imamura K, Kawakami N. Association between meal frequency with others and psychological distress during the COVID-19 pandemic: A cross-sectional study. *Psychiatry Clin Neurosci Rep*. 2022 e61. <https://doi.org/10.1002/pcn5.61>
6. Sugiura K, Morita Y, Kawakami N, Kayama M. How Do Psychiatrists in Japan Choose Involuntary Admission, and What Do They Think of Supported Decision Making? A Thematic Analysis of Peer to Peer Interviews. *Community Ment Health J*. 2022 Nov 3. doi: 10.1007/s10597-022-01046-1. Epub ahead of print. PMID: 36327042.
7. Komase Y, Akiyama H, Kawakami N. Effects of the Collective Gratitude on Work Engagement: A Multilevel Cross-sectional Study. *J Occup Environ Med*. 2022 Nov 1;64(11):e729-e735. doi: 10.1097/JOM.0000000000002683. Epub 2022 Aug 20. PMID: 35993606.
8. Tsuno K, Kawakami N, Tsutsumi A, Shimazu A, Inoue A, Odagiri Y, Shimomitsu T. Victimization and witnessing of workplace bullying and physician-diagnosed physical and mental health and organizational outcomes: A cross-sectional study. *PLoS One*. 2022 Oct 26;17(10):e0265863. doi: 10.1371/journal.pone.0265863. PMID: 36288324; PMCID: PMC9603991.
9. Yasuma N, Imamura K, Watanabe K, Iida M, Takano A. Adolescent cannabis use and the later onset of bipolar disorder: protocol for a systematic review and meta-analysis of prospective cohort studies. *Neuropsychopharmacol Rep*. 2022 Oct 25.
10. Obikane E, Watanabe K, Nishi D, Kawakami N. Adverse childhood experiences and personal values in adolescence: a cross-sectional study using community adult samples in Japan. *Pediatr Int*. 2022 Sep 27:e15370. doi: 10.1111/ped.15370. Epub ahead of print. PMID: 36165851.
11. Kuribayashi K, Takano A, Inagaki A, Imamura K, Kawakami N. Effect of stress management based on cognitive-behavioural therapy on nurses as a universal prevention in the workplace: a systematic review and meta-analysis protocol. *BMJ Open*. 2022 Sep 19;12(9):e062516.
12. Nishi D, Imamura K, Watanabe K, Obikane E, Sasaki N, Yasuma N, Sekiya Y, Matsuyama Y, Kawakami N. The preventive effect of internet-based cognitive behavioral therapy for prevention of depression during pregnancy and in the

- postpartum period (iPDP): a large scale randomized controlled trial. *Psychiatry Clin Neurosci*. 2022 Aug 12.
13. Sasaki N, Imamura K, Watanabe K, Hidaka Y, Ando E, Eguchi H, Inoue A, Tsuno K, Komase Y, Iida M, Otsuka Y, Sakuraya A, Asai Y, Iwanaga M, Kobayashi Y, Inoue R, Shimazu A, Tsutsumi A, Kawakami N. The impact of workplace psychosocial factors on menstrual disorders and infertility: a protocol for a systematic review and meta-analysis. *Syst Rev*. 2022 Sep 7;11(1):195.
 14. Sasaki N, Inoue A, Asaoka H, Sekiya Y, Nishi D, Tsutsumi A, Imamura K. The Survey Measure of Psychological Safety and Its Association with Mental Health and Job Performance: A Validation Study and Cross-Sectional Analysis. *Int J Environ Res Public Health*. 2022 Aug 11;19(16):9879.
 15. Sasaki N, Kuroda R, Tsuno K, Imamura K, Kawakami N. COVID-19 vaccination did not improve employee mental health: A prospective study in an early phase of vaccination in Japan. *Neuropsychopharmacol Rep*. 2022 Jun;42(2):230-232.
 16. Kawakami N, Kim Y, Saito M, Fujishiro S. People's worry about long-term impact of COVID-19 pandemic on mental health. *Asian J Psychiatr*. 2022 Sep;75:103196. doi: 10.1016/j.ajp.2022.103196. Epub 2022 Jun 24. PMID: 35816936; PMCID: PMC9232257.
 17. Takano A, Miyamoto Y, Shinozaki T, Matsumoto T, Kawakami N. Effects of a web-based relapse prevention program on abstinence: Secondary subgroup analysis of a pilot randomized controlled trial. *Neuropsychopharmacol Rep*. 2022 Sep;42(3):362-367. doi: 10.1002/npr2.12272. Epub 2022 Jun 11. PMID: 35689457; PMCID: PMC9515705.
 18. Kessler RC, Kazdin AE, Aguilar-Gaxiola S, Al-Hamzawi A, Alonso J, Altwaijri YA, Andrade LH, Benjet C, Bharat C, Borges G, Bruffaerts R, Bunting B, de Almeida JMC, Cardoso G, Chiu WT, Cía A, Ciutan M, Degenhardt L, de Girolamo G, de Jonge P, de Vries YA, Florescu S, Gureje O, Haro JM, Harris MG, Hu C, Karam AN, Karam EG, Karam G, Kawakami N, Kiejna A, Kovess-Masfety V, Lee S, Makanjuola V, McGrath JJ, Medina-Mora ME, Moskalewicz J, Navarro-Mateu F, Nierenberg AA, Nishi D, Ojagbemi A, Oladeji BD, O'Neill S, Posada-Villa J, Puac-Polanco V, Rapsey C, Ruscio AM, Sampson NA, Scott KM, Slade T, Stagnaro JC, Stein DJ, Tachimori H, Ten Have M, Torres Y, Viana MC, Vigo DV, Williams DR, Wojtyniak B, Xavier M, Zarkov Z, Ziobrowski HN; WHO World Mental Health Survey collaborators. Patterns and correlates of patient-reported helpfulness of treatment for common mental and substance use disorders in the WHO World Mental Health Surveys. *World Psychiatry*. 2022 Jun;21(2):272-286. doi: 10.1002/wps.20971. PMID: 35524618; PMCID: PMC9077614.
 19. Eiko Ozasa, Asuka Sakuraya, Yasuto Sato, Sachiko Takehara, Noriko Kojimahara. How Doctors in Charge of Medical Education Recognize and Use Clinical Practice Guidelines in Education: A Cross-Sectional Study. *Tokyo Women's Medical University Journal* <https://doi.org/10.24488/twmuj>.
 20. Yang CC, Watanabe K, Kawakami N. The Associations Between Job Strain, Workplace PERMA Profiler, and Work Engagement. *J Occup Environ Med*. 2022 May 1;64(5):409-415. doi: 10.1097/JOM.0000000000002455. Epub 2021 Dec 6. PMID: 34873133.

Department of Prevention of Diabetes and Lifestyle-Related Diseases

Project Associate Professor

Satoko Yamaguchi, M.D., Ph.D.

Project Lecturer

Akira Okada, M.D., Ph.D.

※The following information is the same as that of the previous year for certain reasons.

Homepage <https://plaza.umin.ac.jp/prev/>

Introduction and Organization

The Department of Prevention of Diabetes and Lifestyle-Related Diseases is a Social Cooperation Program founded in April 2018, which is sponsored by Asahi Mutual Life Insurance Company and is cooperating with the Department of Nephrology and Endocrinology (Professor Masaomi Nangaku) and Department of Diabetes and Metabolic Diseases (Professor Toshimasa Yamauchi).

The objective of our department is to undertake research on preventing onset and progression of diabetes and other lifestyle-related diseases, through analyses of big data including medical databases and usage of information and communication technology (ICT), thereby making a contribution to improving health of people in Japan.

Lifestyle-related diseases including diabetes account for approximately 30% of medical expenses and 60% of deaths. Moreover, Japan is facing an unprecedented super aged society with aging rate of 28.1% in 2018, and an increasing number of people require long-term care due to conditions caused by lifestyle-related diseases. Analyzing factors associated with onset and progression of lifestyle-related diseases is expected to contribute to preventing lifestyle-related diseases and conditions

caused by them, decreasing the number of people requiring long-term care, as well as optimizing medical expenses.

Our department intends to conduct multidirectional analyses of big data including medical databases and construct models predicting progression of lifestyle-related diseases.

We are receiving four collaborative researchers from Asahi Mutual Life Insurance Company.

Research activities

The members of our department are working on the following research topics.

1) Research on long-term care

An increasing number of people require long-term care in recent years, and as of 2022, approximately 6.9 million people have been certified as being in need for long-term care in Japan. However, factors and diseases leading to conditions requiring long-term care remain largely unknown. In order to identify factors predicting conditions requiring long-term care, we obtained and have analyzed anonymized data of Comprehensive Survey of Living Conditions, a nationwide survey containing household situation and health-related questions, from Ministry of Health,

Labor and Welfare.

2) Research on discontinuation of physician visit in people with diabetes

Discontinuation of diabetes care is associated with increased rate of complications and mortality. We analyzed JMDC database and showed that guideline-recommended practices within the first month of physician consultation for diabetes care can decrease subsequent discontinuation of physician visits in patients with newly diagnosed diabetes.

Additionally, we developed a machine-learning model for predicting people's failure to attend a follow-up visit for diabetes care after recommendations from a national screening program.

3) Research on impact of the COVID-19 pandemic on healthcare service use and health check-ups

The COVID-19 pandemic disrupted healthcare service and health check-ups globally, especially at its beginning. We investigated the impact of pandemic on healthcare service use by analysing hospital-based claims database.

In addition, we investigated the impact of pandemic on health check-ups by conducting a nationwide survey targeting health check-up facilities, in collaboration with Japan Society of Ningen Dock.

This work was supported by MHLW Special Research (Program Grant Number JPMH20CA2046) and Research on Emerging and Re-emerging Infectious Diseases and Immunization (Program Grant Number JPMH21HA2011).

4) Research on bleeding complications after liver biopsy and kidney biopsy in pediatric patients

Little has been reported about bleeding complications after liver or kidney biopsy in pediatric patients. Using a nationwide inpatient database, we investigated major complications after liver biopsy or kidney biopsy in pediatric patients.

We performed research using DPC database and JMDC database in collaboration with the Department of Clinical Epidemiology and Health Economics (Professor Hideo Yasunaga) and medical information database of the University of Tokyo Hospital in collaboration with the Department of Biomedical

Informatics (Professor Kazuhiko Ohe).

In addition to moving these projects forward, we plan to take on new projects using databases in the future.

References

1. Okada A, Yamana H, Yamaguchi S, Kurakawa KI, Michihata N, Matsui H, Fushimi K, Nangaku M, Yamauchi T, Yasunaga H, Kadowaki T. Effect of Branched-Chain Amino Acid Infusion on In-Hospital Mortality of Patients With Hepatic Encephalopathy and End-Stage Kidney Disease: A Retrospective Cohort Study Using a National Inpatient Database. *J Ren Nutr.* 2022;32(4):432-440.
2. Okada A, Hashimoto Y, Goto T, Yamaguchi S, Ono S, Ikeda Kurakawa K, Nangaku M, Yamauchi T, Yasunaga H, Kadowaki T. A Machine Learning-Based Predictive Model to Identify Patients Who Failed to Attend a Follow-up Visit for Diabetes Care After Recommendations From a National Screening Program. *Diabetes Care.* 2022;45(6):1346-1354.
3. Yamaguchi S, Okada A, Sunaga S, Ikeda Kurakawa K, Yamauchi T, Nangaku M, Kadowaki T. Impact of COVID-19 pandemic on healthcare service use for non-COVID-19 patients in Japan: retrospective cohort study. *BMJ Open.* 2022;12(4):e060390.
4. Kurakawa KI, Okada A, Bessho K, Jo T, Ono S, Michihata N, Kumazawa R, Matsui H, Fushimi K, Yamaguchi S, Yamauchi T, Nangaku M, Kadowaki T, Yasunaga H. Major complications after percutaneous biopsy of native or transplanted liver in pediatric patients: a nationwide inpatient database study in Japan. *BMC Gastroenterol.* 2022;22(1):395.
5. Okada A, Yamaguchi S, Jo T, Yokota I, Ono S, Ikeda Kurakawa K, Nangaku M, Yamauchi T, Kadowaki T. Impact of body mass index on in-hospital mortality in older patients hospitalized for bacterial pneumonia with non-dialysis-dependent chronic kidney disease. *BMC Geriatr.* 2022;22(1):950.
6. Okada A, Yamada G, Kimura T, Hagiwara Y, Yamaguchi S, Kurakawa KI, Nangaku M,

Yamauchi T, Matsuyama Y, Kadowaki T. Diagnostic ability using fatty liver and metabolic markers for metabolic-associated fatty liver disease stratified by metabolic/glycemic abnormalities. *J Diabetes Investig*. 2022.

7. Okada A, Ikeda Kurakawa K, Harita Y, Shimizu A, Yamaguchi S, Aso S, Ono S, Hashimoto Y, Kumazawa R, Michihata N, Jo T, Matsui H, Fushimi K, Nangaku M, Yamauchi T, Yasunaga H, Kadowaki T. Comparison of bleeding complications after pediatric kidney biopsy between intravenous sedation and general anesthesia: a nationwide cohort study. *BMC Pediatr*. 2023;23(1):33.

Department of Pain and Palliative Medical Sciences

Project Associate Professor

Maiko Hasegawa-Moriyama, M.D., Ph.D.

Project Assistant Professor

Kirio Kawai, M.D

Homepage N/A

History and outline of organization

About a half of the cancer patients die by cancer though of the recent innovations of anti-cancer treatments. It mainly depends on the efficacy of the first-line strategies whether cancer is curable or not. Almost all the cancer patients whose initial treatment was unsuccessful die after the distressing struggle against their disease within several years. It is clear for such patients that both sufficient anti-cancer treatments and appropriate approaches to improve their quality of life (QOL) are simultaneously indispensable.

However, in our nation, most attention has been entirely paid to the improvement of cure rate and survival time of cancer patients. On the other hand, we have to consider that their QOL is scarcely concentrated until quite recently.

Palliative care means the combination of active therapeutic approach and total human care for the patients no matter which their cancer does or does not respond to anti-cancer treatments. Pain relief, other symptom management, psychological, social and spiritual cares are as a top priority for these patients. It is also emphasized that palliative care is necessary to be applied in the cancer treatment even for patients in early stage of their diseases as well as the progressive or terminal phase of their clinical courses.

In Department of Pain and Palliative Medicine Science, The University of Tokyo Hospital, we participate in pain and palliative care team and takes a leading role not only to control physical symptoms of cancer

patients but also to care for the mental and social support at the same time, and to improve the overall QOL of patients.

Palliative care is described clearly in the law "Cancer Control Act" approved by the National Diet on June 2006 that "The medical treatment to aim at relieving many kinds of pain and problems of cancer patients is applicable from the early course of the illness".

However, it is possible that the use of analgesic, especially opioids are not sufficient for cancer pain in Japan. Therefore, this department work on development and distribution of pain screening tool and educational program. According to our recent study, the nationwide adequacy of opioid availability was approximately 75%, and the largest gaps in adequacy between prefectures were more than 65%, suggesting that opioid might not be adequately prescribed nationwide.

Therefore, we analyze the correlation between cancer pain severity and opioid availability using medical big data to reduce this regional disparity.

Based on these background and purpose, the department was founded in May, 2021.

Consultation

In The University of Tokyo Hospital, we pain and palliative care team are composed of many kinds of specialists containing three full-time staff doctors, two full-time doctors, and two certificated cancer and hospice care nurses who take an initiative in this

multidisciplinary team. We visit to bedsides, consultation rooms and everywhere in the hospital, and offer palliative care to cancer patients who have received cancer care in cooperation with patients' attending doctors, ward staff, therapists of rehabilitation, social workers and every kind of professionals.

Education

In the Department of Pain and Palliative Medicine, junior residents of the first and second year can learn the basic knowledge and practice of palliative care by selecting an optional subject for one, two, four or eight months. And then they can participate in the pain and palliative care team and attend the daily team-conference on weekdays.

Educational

- In the intensive course for the first-year residents, we prepare lectures about:
 - # pain management
 - # diagnoses and management of delirium
 - # Introduction of guidelines in the field of palliative medicine and their use
 - # Basic medication for palliative care
 - # Spirituality and whole person care for Japanese patients facing death

Daily and weekly schedule

- Conference: Monday-Friday (every weekday); 9:00-10:30am
- Consultation: Monday-Friday (every weekday); from the end of morning conference, up to the completion of all the requested consulting of the day.
- The cancer registry: They input data in the ward round with the HIS (Hospital information system) terminal on each floor.

Research

The clinical information accumulated from the palliative care consultation and anesthesia for patients undergoing cancer surgery is input to the concise database simultaneously and utilized for various kinds of clinical researches to submit to the international medical journal.

To date, we the Department of Palliative Medical Sciences have contributed to the progress of following

fields of investigations.

- ① Opioid availability for the palliative care of patients with advanced cancer is increasing globally. However, opioid consumption in Japan is still extremely low compared with that in other countries. We investigated the current situation of pain control and opioid consumption in patients with advanced cancer by a nationwide questionnaire survey in Japan. Caregivers from 2000 comprehensive support centres nationwide answered the web-based questionnaire survey asking for details about their assigned patients who died of end-stage cancer. The survey included the questionnaire of pain intensity and opioid prescription.
- ② In clinical situation, the use of opioids frequently induce delirium. As a result, the use of opioids can be avoided although pain control is not sufficient. Therefore, we investigate the methods for diagnostic tool for delirium and its mechanisms.

Publications

1. Abe H, Sumitani M, Matsui H, Inoue R, Fushimi K, Uchida K, Yasunaga H. Association between hospital palliative care team intervention volume and patient outcomes. *Int J Clin Oncol* 2024; **29**: 1602-9
2. Hasegawa-Moriyama M, Morioka Y, Hiroi S, Naya N, Suzuki Y, Koretake Y, Hara E, Abe H, Uchida K, Sumitani M. High prevalence of severe pain is associated with low opioid availability in patients with advanced cancer: Combined database study and nationwide questionnaire survey in Japan. *Neuropsychopharmacology Reports* 2024; **44**: 502-11
3. Tsuchiya T, Miyawaki S, Saito K, Yoshimoto S, Segawa M, Ebisawa K, Nishikawa M, Sumitani M, Kurokawa M, Yatomi Y, Saito Y. Associations of refractory spontaneous intracranial hypotension and chronic subdural hematoma with factor XIII deficiency: a case report. *Asian J Neurosurgery* 2024 (*in press*)
4. Saita K, Sumitani M, Koyama Y, Sugita S, Matsubayashi Y, Ogata T, Ohtsu H, Chikuda H. Neuropathic pain development and maintenance

and its association with motor recovery after cervical spinal cord injury. *J Spinal Cord Med* **2024** (*in press*)

5. Kurisu K, Inada S, Maeda I, Nobata H, Ogawa A, Iwase S, Uchida M, Akechi T, Amano K, Nakajima N, Morita T, Sumitani M, Yoshiuchi K. Effectiveness of antipsychotics for managing agitated delirium in patients with advanced cancer: a secondary analysis of a multicenter prospective observational study in Japan (Phase-R). *Support Care Cancer* **2024**; **32**: 147
6. Minato T, Kawai K, Edamura T, Abe H, Sumitani M. A case of secondary trigeminal neuralgia caused by lung adenocarcinoma metastasis on trigeminal nerve roots, which was successfully relieved by opioids. *Mol Clin Oncol* **2024**; **20**: 26
7. Osumi M, Sumitani M, Iwatsuki K, Hoshiyama M, Imai R, Morioka S, Hirata H. Resting-state electroencephalography microstates correlate with pain intensity with complex regional pain syndrome. *Clin EEG Neurosci* **2024**; **55**: 121-9
8. Sumitani M, Kimura A, Mochizuki T, Akiyama T, Uranbileg B, Takahashi T, Hirai T, Hayakawa K, Chikuda H, Kurano M. Cerebrospinal fluid lysophosphatidylcholine species for distinguishing narrowing of the lumbar spine. *World Neurosurgery* **2024**; **S1878-8750(23)01881-8**
9. Uragami S, Osumi M, Sumitani M, Fuyuki M, Igawa Y, Iki S, Koga M, Tanaka Y, Sato G, Morioka S. Prognosis of post-stroke pain during rehabilitation depends on the pain quality. *Phys Ther* **2024**; **104**: pzae055
10. Uranbileg B, Sakai E, Kubota M, Isago H, Sumitani M, Yatomi Y, Kurano M. Development of an advanced liquid chromatography-tandem mass spectrometry measurement system for simultaneous shipngolipid analysis. *Scientific Reports* **2024**; **14**: 5699

(And, 12 Japanese articles)

Department of Nutritional Epidemiology and Behavioural Nutrition

Project Professor

Kentaro Murakami, Ph.D.

Project Associate Professor

Nana Shinozaki, R.D., Ph.D.

Homepage <https://www.nebn.m.u-tokyo.ac.jp/nebn/>

Introduction and Organization

The Department of Nutritional Epidemiology and Behavioural Nutrition was established on May 1, 2023, funded by Ajinomoto Co., Ltd. The main purpose is to elucidate various food-related phenomena using a wide variety of food measurement tools and databases and epidemiological methods in order to promote evidence-based improvement plans tailored to each individual on a global level by identifying potential factors that can promote healthy food change through scientific food-related research, including dietary behavior, for the purpose of extending people's healthy life span and well-being.

The cooperating departments are the Department of Health and Social Behavior (Professor Hideki Hashimoto) and the Department of Social Preventive Epidemiology (Professor Kentaro Murakami).

The members are Kentaro Murakami, Project Professor (appointed in May 2023, retired at the end of July), and Nana Shinozaki, Project Assistant Professor (appointed in May 2023).

Research activities

The research in this department is guided by the following:

1) Epidemiological analysis of food-related behaviors and attitudes through measurement and data, using

existing and newly constructed databases to analyze correlations and detect factors of healthy and unhealthy behaviors.

2) Development of new dietary questionnaires and personalized nutritional advice return methods, including a nutritional profiling system that promotes changes in food-related behaviors that achieve people's health.

3) Validation and nutritional epidemiological analysis of dietary surveys in conjunction with health screening fields.

References

1. Shinozaki N, Murakami K, Masayasu S, Sasaki S. Usual Nutrient Intake Distribution and Prevalence of Nutrient Intake Inadequacy among Japanese Children and Adults: A Nationwide Study Based on 8-Day Dietary Records. *Nutrients*. 2023 Dec 14;15(24):5113. doi: 10.3390/nu15245113..
2. Shinozaki N, Murakami K, Yuan X, Tajima R, Matsumoto M, Asakura K, Masayasu S, Sasaki S. The association of highly processed food consumption with food choice values and food literacy in Japanese adults: a nationwide cross-sectional study. *Int J Behav Nutr Phys Act*. 2023 Dec 5;20(1):143.
3. Sugimoto M, Asakura K, Mori S, Shinozaki N, Murakami K, Imamura H, Nishiwaki Y. The

Nutritional Characteristics of Usual Lunches Consumed Among Japanese Workers: Comparison Between Different Lunch-Type Groups. *J Occup Environ Med*. 2024 Jan 1;66(1):e17-e25.

4. Fujiwara A, Fukunaga A, Murakami K, Inoue Y, Nakagawa T, Yamamoto S, Konishi M, Mizoue T. Cross-Sectional Association between Estimated Hardness of the Habitual Diet and Depressive Symptoms in Older Japanese Men. *Nutrients*. 2023 Jul 4;15(13):3034.

Department of Precision Medicine Neurology

Project Associate Professor

Jun Mitsui, M.D., Ph.D.

Introduction and Organization

The Department of Precision Medicine Neurology was established on September 1, 2022, with the aim of applying state-of-the-art genome sequencing technology to elucidate the molecular mechanisms, and to develop novel therapies that can intervene against the molecular mechanisms of neurological diseases.

Clinical activities

Specialized outpatient clinics for multiple system atrophy are provided in collaboration with the Department of Neurology. The outpatient clinic provides consultations, second opinions, and patient registration for patients with multiple system atrophy. In the ward, we provide consultation for the examination and treatment of patients with multiple system atrophy in cooperation with the Department of Neurology. Clinical sequencing is performed after consultation for the diagnosis of hereditary neurological diseases.

Teaching activities

As for under-graduate education, we provides lectures on genetic research and therapeutic development for neurological diseases. In postgraduate education, we collaborates with the Department of Neurology to provide education on the genetic diseases to residents. Regarding graduate education, we promotes a wide range of research according to the wishes of graduate students.

Research activities

Multiple system atrophy is a neurodegenerative disease that causes a variety of symptoms, including autonomic nervous system disturbances, cerebellar ataxia, and parkinsonism. It is an intractable disease for which effective treatments are lacking, although there are drugs that alleviate several symptoms. We are conducting basic research on multiple system atrophy and its treatment to overcome this disease.

In previous studies, we identified patients with biallelic variants in the COQ2 gene in multiplex families (Mitsui J, et al. *N Engl J Med.* 2013;369:233-44). It has been shown that coenzyme Q10 level in cerebellar tissue is decreased in patients with familial multiple system atrophy who have biallelic COQ2 variants (Mitsui J, et al. *N Engl J Med.* 2013; 369:233-44), and that coenzyme Q10 administration improves the rate of cerebral oxygen metabolism (Mitsui J, et al. *Cerebellum.* 2017;16(3):664-672).

Furthermore, the carrier frequency of the COQ2 variant is higher in patients with sporadic multiple system atrophy (Porto KJ, et al. *J Neurol Sci.* 2021; 429:117623), and blood coenzyme Q10 level is decreased even in patients without COQ2 variants (Mitsui J, et al. *JAMA Neurol.* 2016;73(8):977-80). Based on these results, we believe that coenzyme Q10 supplementation may be an effective treatment for this disease.

First, an investigator-initiated Phase 1 trial (UMIN000016695) was conducted to investigate safety and pharmacokinetics of coenzyme q10 (Mitsui

J, et al. *Neurol Clin Neurosci*. 2022;10(1):14-24). A multicenter, investigator-initiated Phase 2 trial (UMIN000031771) was subsequently conducted to explore whether coenzyme Q10 is effective against symptom progression in multiple system atrophy (Mitsui J, et al. *EClinicalMedicine*. 2023 Apr 14;59:101920). Based on the results, a Phase 3 trial is currently being planned.

The Multiple System Atrophy Registry has been established and is being operated to assist in patient recruitment in clinical trials and to obtain natural history of multiple system atrophy (<https://msajp.org/>).

Other than the COQ2 gene, we have reported that GBA1 variants were associated with multiple system atrophy (Mitsui J, et al. *Ann Clin Transl Neurol*. 2015; 2(4):417-26).

References

1. Teranishi Y, Miyawaki S, Nakatochi M, Okano A, Ohara K, Hongo H, Ishigami D, Sakai Y, Shimada D, Takayanagi S, Ikemura M, Komura D, Katoh H, Mitsui J, Morishita S, Ushiku T, Ishikawa S, Nakatomi H, Saito N. Meningiomas in patients with neurofibromatosis type 2 predominantly comprise 'immunogenic subtype' tumours characterised by macrophage infiltration.
2. Orimo K, Kakumoto T, Hara R, Goto R, Ishiura H, Mitsui J, Yoshida C, Uesaka Y, Suzuki Y, Morishita S, Satake W, Tsuji S, Toda T. A Japanese family with idiopathic basal ganglia calcification carrying a novel XPR1 variant. *J Neurol Sci*. 2023 Aug 15;451:120732. doi: 10.1016/j.jns.2023.120732.
3. Nakahara Y, Mitsui J, Date H, Porto KJ, Hayashi Y, Yamashita A, Kusakabe Y, Matsukawa T, Ishiura H, Yasuda T, Iwata A, Goto J, Ichikawa Y, Momose Y, Takahashi Y, Toda T, Ohta R, Yoshimura J, Morishita S, Gustavsson EK, Christy D, Maczys M, Farrer MJ, Kim HJ, Park SS, Jeon B, Zhang J, Gu W, Scholz SW, Singleton AB, Houlden H, Yabe I, Sasaki H, Matsushima M, Takashima H, Kikuchi A, Aoki M, Hara K, Kakita A, Yamada M, Takahashi H, Onodera O, Nishizawa M, Watanabe H, Ito M, Sobue G, Ishikawa K, Mizusawa H, Kanai K, Kuwabara S, Arai K, Koyano S, Kuroiwa Y, Hasegawa K, Yuasa T, Yasui K, Nakashima K, Ito H, Izumi Y, Kaji R, Kato T, Kusunoki S, Osaki Y, Horiuchi M, Yamamoto K, Shimada M, Miyagawa T, Kawai Y, Nishida N, Tokunaga K, Dürr A, Brice A, Filla A, Klockgether T, Wüllner U, Tanner CM, Kukull WA, Lee VM, Masliah E, Low PA, Sandroni P, Ozelius L, Foroud T, Tsuji S. Genome-wide association study identifies a new susceptibility locus in PLA2G4C for Multiple System Atrophy. *medRxiv [Preprint]*. 2023 May 2:2023.05.02.23289328. doi: 10.1101/2023.05.02.23289328.
4. Mitsui J, Matsukawa T, Uemura Y, Kawahara T, Chikada A, Porto KJL, Naruse H, Tanaka M, Ishiura H, Toda T, Kuzuyama H, Hirano M, Wada I, Ga T, Moritoyo T, Takahashi Y, Mizusawa H, Ishikawa K, Yokota T, Kuwabara S, Sawamoto N, Takahashi R, Abe K, Ishihara T, Onodera O, Matsuse D, Yamasaki R, Kira JI, Katsuno M, Hanajima R, Ogata K, Takashima H, Matsushima M, Yabe I, Sasaki H, Tsuji S. High-dose ubiquinol supplementation in multiple-system atrophy: a multicentre, randomised, double-blinded, placebo-controlled phase 2 trial. *EClinicalMedicine*. 2023 Apr 14;59:101920. doi: 10.1016/j.eclinm.2023.101920.
5. Naruse H, Okubo S, Sudo A, Mitsui J, Mikata T, Ishiura H, Morishita S, Tsuji S, Toda T. Clinical features of a family with late-onset distal hereditary motor neuropathy harboring p.Pro39Leu variant of HSPB1. *J Peripher Nerv Syst*. 2023 Sep;28(3):518-521. doi: 10.1111/jns.12567.
6. Kuroda Y, Saito Y, Enomoto Y, Naruto T, Mitsui J, Kurosawa K. PHACES-like syndrome with TMEM260 compound heterozygous variants. *Am J Med Genet A*. 2023 Aug;191(8):2215-2218. doi: 10.1002/ajmg.a.63245.
7. Kawamoto N, Hamada Y, Kobayashi S, Naruse H, Ishiura H, Matsukawa T, Mitsui J, Tsuji S, Sonoo M, Toda T. Noncanonical splice-site variant in peripheral myelin protein 22 gene (PMP22) in a patient with hereditary neuropathy with liability to pressure palsies. *J Peripher Nerv Syst*. 2023 Sep;28(3):513-517. doi: 10.1111/jns.12558.

8. Mitsutake A, Matsukawa T, Iwata A, Ishiura H, Mitsui J, Mori H, Toya T, Honda A, Kurokawa M, Sakai N, Tsuji S, Toda T. Favorable outcome of hematopoietic stem cell transplantation in late-onset Krabbe disease. *Brain Dev.* 2023 Aug; 45(7):408-412. doi: 10.1016/j.braindev.2023.04.001.
9. Takegami N, Mitsutake A, Mano T, Shintani-Domoto Y, Unuma A, Yamaguchi-Takegami N, Ishiura H, Sakuishi K, Ando M, Yamauchi H, Ono M, Morishita S, Mitsui J, Shimizu J, Tsuji S, Toda T. The Myocardial Accumulation of Aggregated Desmin Protein in a Case of Desminopathy with a de novo DES p.R406W Mutation. *Intern Med.* 2023 Oct 1;62(19):2883-2887. doi: 10.2169/internalmedicine.0992-22.
10. Hama Y, Date H, Fujimoto A, Matsui A, Ishiura H, Mitsui J, Yamamoto T, Tsuji S, Mizusawa H, Takahashi Y. A Novel de novo KIF1A Mutation in a Patient with Ataxia, Intellectual Disability and Mild Foot Deformity. *Cerebellum.* 2023 Dec;22(6):1308-1311. doi: 10.1007/s12311-022-01489-y.
11. Ueda M, Katsuse K, Kakumoto T, Kobayashi S, Ishiura H, Mitsui J, Toda T. Copper Deficiency in Wilson's Disease with a Normal Zinc Value. *Intern Med.* 2023 Apr 1;62(7):1073-1076. doi: 10.2169/internalmedicine.9366-22.
12. Hongo H, Miyawaki S, Teranishi Y, Mitsui J, Katoh H, Komura D, Tsubota K, Matsukawa T, Watanabe M, Kurita M, Yoshimura J, Dofuku S, Ohara K, Ishigami D, Okano A, Kato M, Hakuno F, Takahashi A, Kunita A, Ishiura H, Shin M, Nakatomi H, Nagao T, Goto H, Takahashi SI, Ushiku T, Ishikawa S, Okazaki M, Morishita S, Tsuji S, Saito N. Somatic GJA4 gain-of-function mutation in orbital cavernous venous malformations. *Angiogenesis.* 2023 Feb;26(1):37-52. doi: 10.1007/s10456-022-09846-5.

Department of Health Services Research

Project Associate Professor

Taisuke Jo, M.D., Ph.D.

Project Lecturer/Project Assistant Professor

Hayato Yamana, M.D., PhD.

Project Assistant Professor

Nobuaki Michihata, M.D., PhD.

※The following information is the same as that of the previous year for certain reasons.

Homepage <http://webpark1902.sakura.ne.jp/wp/>

Introduction and Organization

The Department of Health Services Research (HSR), a Social Cooperation Program, was founded by Professor Hideo Yasunaga, Department of Clinical Epidemiology & Health Economics with the support of Professor Takahide Nagase, Department of Respiratory Medicine in April 2016. The program was funded by Tsumura & Co., Tokyo, Japan.

The objective of the Department of HSR was to convey and develop HSR, which encompasses clinical medicine, clinical epidemiology and health economics, to pursue the maintenance of health services particularly in the ageing society in Japan. Education and training of personnel to cultivate human resources such as researchers and analysts in HSR is another important mission of this program.

The founding staff members were Taisuke Jo (Project Associate Professor), Nobuaki Michihata (Project Assistant Professor) and Yusuke Sasabuchi (Project Assistant Professor). Hayato Yamana (Project Assistant Professor) started to take part in this program in April 2018 with two other staff members, Taisuke Jo and Nobuaki Michihata. Hayato Yamana was promoted to Project Lecturer in 2021 and resigned at the end of November 2022.

Teaching activities

All the members of HSR participated in the lectures of Clinical Epidemiology, a curriculum of School of Public Health (SPH) in The University of Tokyo. The members also contributed to the education and training of individual students of SPH as well as students of the Graduate School of Medicine, The University of Tokyo.

Taisuke Jo (Project Associate Professor) participated in the series of clinical lectures in Respiratory Medicine for students of Faculty of Medicine, The University of Tokyo.

Research activities

Health Services Research covers a broad cross-disciplinary field involving studies of structures, processes and outcomes assessment in clinical epidemiology and health services, studies evaluating the quality of health care and analysis of health economics, finance and allocation of medical resources. Utilizing large databases, the members of HSR were working to address the following issue.

1) Clinical and epidemiological research questions related to various diseases, including respiratory disease.

- 2) Outcomes and cost-effectiveness in both western medicine and eastern medicine in Japan.
- 3) Impact of super-ageing society on population dynamics and demand for health services.
- 4) Efficient distribution of medical staff, medical institutions, and armamentariums.

The following are the examples of studies conducted in 2022. More than 72 articles were published.

- 1) Recombinant human soluble thrombomodulin for acute exacerbation of idiopathic pulmonary fibrosis: a nationwide observational study

Background: Acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) is the leading cause of death among patients with IPF. However, there is no established treatment for this condition. Hence, we aimed to investigate the effectiveness and safety of recombinant human soluble thrombomodulin (rTM) for the treatment of AE-IPF. **Methods:** Data were retrospectively collected from the Japanese Diagnosis Procedure Combination database from 1 January 2014 to 31 March 2018. We identified adult patients with IPF who received high-dose methylprednisolone (mPSL) therapy and mechanical ventilation upon admission. Eligible patients ($n = 2814$) were divided into those receiving high-dose mPSL alone (mPSL alone group, $n = 2602$) and rTM combined with high-dose mPSL (rTM group, $n = 212$). A stabilised inverse probability of treatment weighting (IPTW) using propensity scores was performed to compare outcomes between the two groups. The primary outcome was in-hospital mortality, and the secondary outcomes were 14- and 28-day mortality, bleeding events and length of hospital stay. **Results:** The in-hospital mortality rates of the mPSL alone and rTM groups were 75.9% and 76.9%, respectively. The results did not significantly differ between the two groups after performing a stabilised IPTW. The odds ratio of the rTM group compared to the mPSL alone group was 1.15 (95% confidence interval: 0.71–1.84; $p = 0.57$). Moreover, the secondary outcomes did not differ significantly between the two groups. **Conclusions:** In patients with AE-IPF who developed severe respiratory failure, rTM in addition to high-dose mPSL was not associated with a better outcome.

- 2) Safety of topical ophthalmic antibiotics in pregnant women with hordeola, chalazia, blepharitis, or bacterial conjunctivitis: propensity score analyses

Objective: To investigate the association between exposure to topical ophthalmic antibiotics during pregnancy and adverse neonatal outcomes. **Methods:** In this retrospective cohort study, we identified pregnant women with hordeola, chalazia, blepharitis, or bacterial conjunctivitis from 2005 to 2018 using the Japanese Medical Data Centre Claims Database. From the eligible women, we extracted women who were dispensed no topical antibiotics during the first trimester (non-antibiotic group), women who were dispensed topical fluoroquinolones alone at least once (fluoroquinolone alone group), and women who were dispensed any single type of antibiotic (single-antibiotic group). We compared the frequency of congenital anomalies (CA), preterm birth (PB), low birth weight (LBW), and the composite outcome of these three between the fluoroquinolone and nonantibiotic groups and between the single-antibiotic and non-antibiotic groups, using propensity score adjustment. **Results:** A total of 891 eligible women were identified. In the fluoroquinolone ($n = 409$) and non-antibiotic ($n = 309$) groups, CA occurred in 6.8% and 6.8%, PB in 2.4% and 3.2%, LBW in 2.9% and 3.2%, and the composite outcome in 10.5% and 11.3%, respectively. Analysis using propensity score adjustment showed no significant difference between the groups in the frequency of CA (adjusted odds ratio, 1.15; 95% confidence interval, 0.61–2.18), PB (0.80; 0.30–2.17), LBW (1.08; 0.45–2.63), or the composite outcome (1.12; 0.67–1.87). Comparison of the single-antibiotic and non-antibiotic groups showed similar results. **Conclusions:** Topical ophthalmic antibiotics for hordeola, chalazia, blepharitis, or bacterial conjunctivitis during the first trimester were not associated with increased adverse neonatal outcomes.

- 3) Association between comprehensive geriatric assessment and polypharmacy at discharge in patients with ischaemic stroke: A nationwide, retrospective, cohort study

Background Polypharmacy and its adverse drug events are a major healthcare challenge related to falls, hospitalisations and mortality. Comprehensive

geriatric assessment (CGA) may contribute to polypharmacy improvement, however, there is no clear evidence so far.

Methods Using a national inpatient database in Japan from April 1, 2014 to March 31, 2018, we investigated the association between CGA and polypharmacy. We identified patients aged ≥ 65 years admitted for ischaemic stroke who could receive oral medications. Propensity score matching was conducted for patients with and without CGA during hospitalisation. The outcomes were polypharmacy (defined as use of five or more types of oral medications) at discharge, the number of medication types prescribed at discharge, and the difference between the numbers of medication types prescribed on admission and at discharge.

Findings A total of 162,443 patients were analysed, of whom 39,356 (24.2%) received CGA, and propensity score matching identified 39,349 pairs. Compared with non-CGA group, the CGA group had a significantly lower proportion of polypharmacy at discharge (34.3% vs. 32.9%, $p < 0.001$) and a smaller number of medication types prescribed at discharge (3.84 vs. 3.76, $p < 0.001$).

Interpretation This study shows the clear evidence that there is a positive relationship between CGA and a reduction in the number of medications in older inpatients with ischaemic stroke.

The members of HSR are further mounting an effort to accomplish the task in cooperation with the Department of Clinical Epidemiology & Health Economics and the Department of Respiratory Medicine.

References

(Due to space constraints, only a portion of the publications is listed below.)

- 1: Isogai T, Saad AM, Michihata N, Ahuja KR, Shekhar S, Abdelfattah OM, Kaur M, Gad MM, Svensson LG, Kapadia SR. Association of hospital procedural volume with incidence and outcomes of surgical bailout in patients undergoing transcatheter aortic valve replacement. *Catheter Cardiovasc Interv.* 2022;99:160-168.
- 2: Matsuoka S, Kaneko H, Okada A, Morita K, Itoh H, Michihata N, Jo T, Takeda N, Morita H, Fujiu K, Nakamura S, Node K, Yasunaga H, Komuro I. Age Modified Relationship Between Modifiable Risk Factors and the Risk of Atrial Fibrillation. *Circ Arrhythm Electrophysiol.* 2022;15:e010409.
- 3: Konishi T, Fujiogi M, Michihata N, Niwa T, Morita K, Matsui H, Fushimi K, Tanabe M, Seto Y, Yasunaga H. Impact of body mass index on short-term outcomes after differentiated thyroid cancer surgery: a nationwide inpatient database study in Japan. *Eur Thyroid J.* 2022;11:e210081.
- 4: Suzuki Y, Kaneko H, Okada A, Itoh H, Morita K, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Yamaguchi S, Kamiya K, Matsunaga A, Ako J, Fukui A, Nishiyama A, Yokoo T, Node K, Yamauchi T, Nangaku M, Yasunaga H, Komuro I. Change in Cardiovascular Health Metrics and Risk for Proteinuria Development: Analysis of a Nationwide Population-Based Database. *Am J Nephrol.* 2022;53:240-248.
- 5: Suzuki Y, Kaneko H, Okada A, Itoh H, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Yamaguchi S, Kamiya K, Matsunaga A, Ako J, Node K, Yamauchi T, Nangaku M, Yasunaga H, Komuro I. Impact of Glucose Tolerance and Its Change on Incident Proteinuria: Analysis of a Nationwide Population-Based Dataset. *Am J Nephrol.* 2022;53(4):307-315.
- 6: Nagata S, Ohbe H, Jo T, Matsui H, Fushimi K, Yasunaga H. Glucocorticoids and Rates of Biphasic Reactions in Patients with Adrenaline-Treated Anaphylaxis: A Propensity Score Matching Analysis. *Int Arch Allergy Immunol.* 2022;183:939-945.
- 7: Tamiya H, Mitani A, Abe T, Nagase Y, Suzuki H, Jo T, Tanaka G, Nagase T. Association between Inhalation Instruction Method in Community Pharmacies and Inhaler Device Handling Error in Patients with Obstructive Lung Disease: An Evaluation of the Impact of Practical Demonstration by Pharmacists. *Biol Pharm Bull.* 2022; 45(12):1764-1771.
- 8: Suzuki Y, Kaneko H, Okada A, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Kamiya K, Matsunaga A, Ako J, Node K, Nangaku M, Yasunaga H, Komuro I. Proteinuria and Risk for Heart Failure in 55,191 Patients Having History of Cancer. *Am J Nephrol.* 2022;53:753-760.
- 9: Nomura O, Michihata N, Kaneko K, Yoshikawa T,

- Ishiguro A; Japan Pediatric Society Steering Committee for Board Examinations. Research Publication Experience as a Requirement for Board Examination Acceptance to Promote Scholarly Activities of Pediatric Residents. *JMA J.* 2022;5:93-98.
- 10: Matsui H, Yamana H, Fushimi K, Yasunaga H. Development of Deep Learning Models for Predicting In-Hospital Mortality Using an Administrative Claims Database: Retrospective Cohort Study. *JMIR Med Inform.* 2022;10:e27936.
- 11: Miyakawa T, Michihata N, Morita K, Matsui H, Honda M, Yasunaga H. Ambient temperature and hospital admissions for acute cholecystitis: a nationwide inpatient database study in Japan. *HPB (Oxford).* 2022;24:398-403.
- 12: Hashimoto Y, Matsui H, Michihata N, Ishimaru M, Yasunaga H, Aihara M, Kaburaki T. Incidence of Sympathetic Ophthalmia after Inciting Events: A National Database Study in Japan. *Ophthalmology.* 2022;129:344-352.
- 13: Sugawara C, Yamana H, Sasagawa E, Yonezawa K, Hikita N, Morita K, Matsui H, Yasunaga H, Haruna M. Factors Associated with Surgical Treatment in Postpartum Women with Mastitis or Breast Abscess: A Retrospective Cohort Study. *Breastfeed Med.* 2022;17:233-238.
- 14: Kodama S, Jo T, Yasunaga H, Michihata N, Matsui H, Kumazawa R, Shiota Y, Fushimi K, Toda T, Hamada M. Outcomes of gastrointestinal cancer surgeries in Parkinson's disease patients: A nationwide study. *Parkinsonism Relat Disord.* 2022;96:45-49.
- 15: Awano N, Jo T, Izumo T, Inomata M, Morita K, Matsui H, Fushimi K, Urushiyama H, Nagase T, Yasunaga H. Recombinant human soluble thrombomodulin for acute exacerbation of idiopathic pulmonary fibrosis: a nationwide observational study. *J Intensive Care.* 2022;10:14.
- 16: Ueno K, Kamiya K, Kaneko H, Okada A, Itoh H, Fujii K, Takeda N, Morita H, Michihata N, Jo T, Yasunaga H, Komuro I. Acute-Phase Initiation of Cardiac Rehabilitation for Short-Term Improvement in Activities of Daily Living in Patients Hospitalized for Acute Heart Failure. *J Cardiovasc Dev Dis.* 2022;9:97.
- 17: Konishi T, Goto T, Fujiogi M, Michihata N, Kumazawa R, Matsui H, Fushimi K, Tanabe M, Seto Y, Yasunaga H. New machine learning scoring system for predicting postoperative mortality in gastroduodenal ulcer perforation: A study using a Japanese nationwide inpatient database. *Surgery.* 2022;171:1036-1042.
- 18: Yamana H, Tsuchiya A, Horiguchi H, Morita S, Kuroki T, Nakai K, Nishimura H, Jo T, Fushimi K, Yasunaga H. Validity of a model using routinely collected data for identifying infections following gastric, colon, and liver cancer surgeries. *Pharmacoepidemiol Drug Saf.* 2022;31:452-460.
- 19: Sato M, Yamana H, Ono S, Ishimaru M, Matsui H, Yasunaga H. Trends in prophylactic antibiotic use for tooth extraction from 2015 to 2018 in Japan: An analysis using a health insurance claims database. *J Infect Chemother.* 2022;28:504-509.
- 20: Suzuki Y, Kaneko H, Okada A, Itoh H, Fujii K, Michihata N, Jo T, Takeda N, Morita H, Yamaguchi S, Yano Y, Kamiya K, Matsunaga A, Ako J, Fukui A, Yokoo T, Nishiyama A, Node K, Yamauchi T, Nangaku M, Yasunaga H, Komuro I. Risk for Proteinuria in Newly Defined Hypertensive People Based on the 2017 American College of Cardiology/American Heart Association Blood Pressure Guideline. *Am J Cardiol.* 2022;168:83-89.
- 21: Matsuoka S, Kaneko H, Okada A, Fukui A, Yano Y, Itoh H, Morita K, Fujii K, Michihata N, Jo T, Takeda N, Morita H, Yamaguchi S, Nakamura S, Nishiyama A, Yokoo T, Node K, Yamauchi T, Nangaku M, Yasunaga H, Komuro I. Association between proteinuria and incident colorectal cancer: analysis of a nationwide population-based database. *BMJ Open.* 2022;12:e056250.
- 22: Seike Y, Matsuda H, Shimizu H, Ishimaru S, Hoshina K, Michihata N, Yasunaga H, Komori K; Japanese Committee for Stentgraft Management (JACSM)*. Nationwide Analysis of Persistent Type II Endoleak and Late Outcomes of Endovascular Abdominal Aortic Aneurysm Repair in Japan: A Propensity-Matched Analysis. *Circulation.* 2022;145:1056-1066.
- 23: Honda A, Michihata N, Iizuka Y, Uda K, Morita

- K, Mieda T, Takasawa E, Ishiwata S, Tajika T, Matsui H, Fushimi K, Yasunaga H, Chikuda H. Risk factors for severe lower extremity ischemia following venoarterial extracorporeal membrane oxygenation: an analysis using a nationwide inpatient database. *Trauma Surg Acute Care Open*. 2022;7:e000776
- 24: Hashimoto Y, Michihata N, Yamana H, Shigemi D, Morita K, Matsui H, Yasunaga H, Aihara M. Safety of topical ophthalmic antibiotics in pregnant women with hordeola, chalazia, blepharitis, or bacterial conjunctivitis: propensity score analyses. *Eye (Lond)*. 2022;36:1066-1073.
 - 25: Yoshii K, Michihata N, Hirasawa K, Nagata S, Morisaki N. Secular trends in early motor development between 1980 and 2010 in Japan. *Arch Dis Child*. 2022 May;107(5):468-473.
 - 26: Matsuda K, Jo T, Shimura A, Honda A, Taoka K, Masamoto Y, Matsui H, Fushimi K, Yasunaga H, Kurokawa M. Risk of febrile neutropenia in very elderly patients aged ≥ 80 years receiving their first cycle of R-CHOP regimen: a nationwide real-world study in Japan. *Br J Haematol*. 2022;197:e37-e41.
 - 27: Konishi T, Fujiogi M, Sato A, Michihata N, Kumazawa R, Matsui H, Fushimi K, Tanabe M, Seto Y, Yasunaga H. Short-Term Outcomes Following Breast Cancer Surgery With and Without Neoadjuvant Chemotherapy: A Nationwide Administrative Database Study in Japan. *Ann Surg Oncol*. 2022;29:3000-3010.
 - 28: Suzuki T, Michihata N, Yoshikawa T, Saito K, Matsui H, Fushimi K, Yasunaga H. Low- versus high-concentration intravenous immunoglobulin for children with Kawasaki disease in the acute phase. *Int J Rheum Dis*. 2022;25:576-583
 - 29: Matsuoka S, Kaneko H, Okada A, Itoh H, Suzuki Y, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Nakamura S, Node K, Yasunaga H, Komuro I. Association of retinal atherosclerosis assessed using Keith-Wagener-Barker system with incident heart failure and other atherosclerotic cardiovascular disease: Analysis of 319,501 individuals from the general population. *Atherosclerosis*. 2022;348:68-74.
 - 30: Ueno K, Kaneko H, Kamiya K, Itoh H, Okada A, Suzuki Y, Matsuoka S, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Ako J, Node K, Yamauchi T, Yasunaga H, Komuro I. Relationship of normal-weight central obesity with the risk for heart failure and atrial fibrillation: analysis of a nationwide health check-up and claims database. *Eur Heart J Open*. 2022;2:oeac026
 - 31: Suzuki Y, Kaneko H, Yano Y, Okada A, Itoh H, Matsuoka S, Fujiu K, Yamaguchi S, Michihata N, Jo T, Takeda N, Morita H, Node K, Kim HC, Viera AJ, Oparil S, Yasunaga H, Komuro I. Age-Dependent Relationship of Hypertension Subtypes With Incident Heart Failure. *J Am Heart Assoc*. 2022;11:e025406.
 - 32: Suzuki Y, Kaneko H, Okada A, Itoh H, Matsuoka S, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Kamiya K, Matsunaga A, Ako J, Node K, Yasunaga H, Komuro I. Comparison of cardiovascular outcomes between SGLT2 inhibitors in diabetes mellitus. *Cardiovasc Diabetol*. 2022;21:67.
 - 33: Ohisa K, Yamana H, Morita K, Matsui H, Fushimi K, Yasunaga H. Association between subcutaneous steroid injection for extravasation of vesicant anticancer drugs and skin ulcers requiring surgery. *Eur J Oncol Nurs*. 2022;58:102119.
 - 34: Suzuki Y, Kaneko H, Okada A, Matsuoka S, Itoh H, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Yamaguchi S, Node K, Yamauchi T, Yasunaga H, Komuro I. Prediabetes in Young Adults and Its Association With Cardiovascular Health Metrics in the Progression to Diabetes. *J Clin Endocrinol Metab*. 2022;107:1843-1853.
 - 35: Okada A, Yamana H, Yamaguchi S, Kurakawa KI, Michihata N, Matsui H, Fushimi K, Nangaku M, Yamauchi T, Yasunaga H, Kadowaki T. Effect of Branched-Chain Amino Acid Infusion on In-Hospital Mortality of Patients With Hepatic Encephalopathy and End-Stage Kidney Disease: A Retrospective Cohort Study Using a National Inpatient Database. *J Ren Nutr*. 2022;32:432-440.
 - 36: Konishi T, Fujiogi M, Michihata N, Kumazawa R, Ohbe H, Matsui H, Fushimi K, Ogita M, Tanabe M, Seto Y, Yasunaga H. Interstitial lung disorders following postoperative radiotherapy with concurrent or sequential hormonal therapy for breast cancer: a nationwide database study in

- Japan. Breast Cancer. 2022;29:688-697
- 37: Kumazawa R, Jo T, Matsui H, Fushimi K, Yasunaga H. Direct oral anticoagulants versus warfarin for secondary prevention of cerebral infarction and bleeding in older adults with atrial fibrillation. *J Am Geriatr Soc.* 2022;70:2029-2039.
 - 38: Konishi T, Fujiogi M, Michihata N, Matsui H, Tanabe M, Seto Y, Yasunaga H. Association between body mass index and incidence of breast cancer in premenopausal women: a Japanese nationwide database study. *Breast Cancer Res Treat.* 2022;194:315-325
 - 39: Ueno K, Kaneko H, Kamiya K, Itoh H, Okada A, Suzuki Y, Matsuoka S, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Ako J, Yasunaga H, Komuro I. Clinical utility of simple subjective gait speed for the risk stratification of heart failure in a primary prevention setting. *Sci Rep.* 2022;12:11641.
 - 40: Konishi T, Fujiogi M, Michihata N, Morita K, Matsui H, Fushimi K, Tanabe M, Seto Y, Yasunaga H. Association of Operative Day of the Week with the Length of Stay and Total Hospitalization Costs in Patients with Partial Mastectomy: A Nationwide Database Study in Japan. *JMA J.* 2022;5:319-327.
 - 41: Hashimoto Y, Yamana H, Michihata N, Shigemi D, Ishimaru M, Matsui H, Yasunaga H, Aihara M. Eye drops for dry eye disease during pregnancy and adverse neonatal outcomes: high-dimensional propensity score analyses. *Ophthalmic Epidemiol.* 2022;29:384-393.
 - 42: Kaneko H, Yano Y, Lee HH, Lee H, Okada A, Itoh H, Morita K, Fukui A, Fujiu K, Suzuki Y, Matsuoka S, Nakamura S, Michihata N, Jo T, Takeda N, Morita H, Yokoo T, Nishiyama A, Node K, Viera AJ, Muntner P, Oparil S, Kim HC, Yasunaga H, Komuro I. Medication-Naïve Blood Pressure and Incident Cancers: Analysis of 2 Nationwide Population-Based Databases. *Am J Hypertens.* 2022;35:731-739.
 - 43: Fuseda Y, Michihata N, Kumazawa R, Fushimi K, Yasunaga H. Annual Trend in Lumbar Puncture for Infants Younger Than 3 Months Hospitalized With Suspected Serious Bacterial Infection: A Nationwide Inpatient Database Study. *Pediatr Infect Dis J.* 2022;41:631-635.
 - 44: Michihata N, Suzuki T, Honda A, Oka I, Yoshikawa T, Saito K, Matsui H, Fushimi K, Yasunaga H. Clinical Features of Kawasaki Disease With Atlantoaxial Rotatory Fixation. *Pediatr Infect Dis J.* 2022;41:626-630.
 - 45: Hosoi T, Yamana H, Tamiya H, Matsui H, Fushimi K, Akishita M, Yasunaga H, Ogawa S. Association between comprehensive geriatric assessment and polypharmacy at discharge in patients with ischaemic stroke: A nationwide, retrospective, cohort study. *EClinicalMedicine.* 2022;50:101528
 - 46: Itoh H, Kaneko H, Okada A, Suzuki Y, Fujiu K, Matsuoka S, Michihata N, Jo T, Nakanishi K, Takeda N, Morita H, Node K, Di Tullio MR, Homma S, Yasunaga H, Komuro I. Age-Specific Relation of Cardiovascular Health Metrics With Incident Cardiovascular Disease. *Am J Cardiol.* 2022;177:34-39.
 - 47: Fukui A, Kaneko H, Okada A, Yano Y, Itoh H, Matsuoka S, Morita K, Kiriya H, Kamon T, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Nakamura S, Nishiyama A, Node K, Yokoo T, Nangaku M, Yasunaga H, Komuro I. Semiquantitative assessed proteinuria and risk of heart failure: analysis of a nationwide epidemiological database. *Nephrol Dial Transplant.* 2022;37:1691-1699
 - 48: Kurakawa KI, Okada A, Bessho K, Jo T, Ono S, Michihata N, Kumazawa R, Matsui H, Fushimi K, Yamaguchi S, Yamauchi T, Nangaku M, Kadowaki T, Yasunaga H. Major complications after percutaneous biopsy of native or transplanted liver in pediatric patients: a nationwide inpatient database study in Japan. *BMC Gastroenterol.* 2022;22:395.
 - 49: Honda A, Iizuka Y, Michihata N, Uda K, Mieda T, Takasawa E, Ishiwata S, Kakuta Y, Tomomatsu Y, Ito S, Inomata K, Matsui H, Fushimi K, Yasunaga H, Chikuda H. Effect of Intraoperative Tranexamic Acid on Perioperative Major Hemorrhage Requiring Transfusion in Patients Undergoing Elective Spine Surgery: A Propensity Score-Matched Analysis Using a National Inpatient Database. *Global Spine J.* 2022: 21925682221123317.

Division of Chronic Kidney Disease (CKD) Pathophysiology

Division Chief (Professor)

Reiko Inagi, Ph.D.

Assistant Professor

Sho Hasegawa, M.D., Ph.D.

PhD Students

Yuto Takenaka, M.D. (Division of Nephrology and Endocrinology)

Chigusa Kitayama, M.D. (Division of Nephrology and Endocrinology)

Li Qi, M.D. (Division of Nephrology and Endocrinology)

Madina Saipidin, M.Sc. (Division of Nephrology and Endocrinology)

Visiting Researcher

Yu Ah Hong, M.D., Ph.D. (2023 September –)

Jin Shang, M.D., Ph.D. (2024 February –)

Lab Technician

Ikumi Okuaki, B.S.

Keiko Miyamoto, B.S.

Homepage <http://www.todai-ckd.com>

Introduction and Organization

In Japan, more than 13 million people suffer from chronic kidney disease (CKD), or roughly one in every eight adults. Why has the number of CKD patients increased so remarkably? One major cause is the sharp increase in the number of people with diabetic nephropathy, which is a complication of diabetes; since 1998, this has been the most important cause among diseases which require incipient dialysis in Japan. Additional causes include the aging of society and other social factors. The kidney is called a silent organ, and CKD progresses without subjective symptoms. It is now evident, however, that asymptomatic CKD which progresses over time carries a number of risks.

One risk is the possible progression of CKD to end-stage renal disease (ESRD), which requires renal replacement therapy. A second risk is the development and progression of lifestyle-related diseases, such as heart attack and arteriosclerosis. The kidneys work closely with the heart and other organs, and a decrease in renal function causes dysfunction of the heart and blood vessels. This adverse impact of the progression of CKD on other organs underlines the importance of the kidneys in maintaining general health. Further, many researchers have also focused on the vicious spiral of aging and CKD: aging worsens the progression of CKD, while CKD accelerates aging. With our modern lifestyles and the super-aging society, CKD cannot be separated from lifestyle-related diseases, and senility cannot be separated from CKD.

Creating a healthy, long-lived society full of energy and vigor requires that the quality of life (QOL) of the elderly be improved. In turn, total medical expenditures will also be decreased. These are important issues requiring urgent solutions. Against this background, the Division of CKD Pathophysiology was newly established in November 2013 with support from Kyowa Hakko Kirin Co., Ltd. The aim of the Division is to aid and support the CKD control and the creation of a healthy and long-lived society. The Division takes an innovative approach to identifying the pathophysiology of CKD and works to develop more effective CKD preventive and therapeutic strategies. Through these research activities, our goal is to contribute to the creation of a healthy, long-lived society in which the elderly can live a happy and independent life.

Major Research Projects

The Division of CKD Pathophysiology works in collaboration with the Division of Nephrology and Endocrinology, a part of The University of Tokyo Graduate School of Medicine (Professor Masaomi Nangaku) to conduct basic and clinical research on CKD pathophysiology, including:

- 1) Identifying the mechanism of destruction of adaptive signals to various stresses (endoplasmic reticulum stress, ischemia, glycation stress, oxidative stress) in CKD; and using the findings obtained to establish new CKD treatment strategies.
- 2) Clarifying the mechanism of functional change in renal erythropoietin (EPO)-producing cells, along with the mechanisms of CKD progression and identification of the mechanism of development and progress of renal anemia.
- 3) Clarifying the impact of kidney aging on CKD progression in super-aging society
- 4) Identifying factors in the exacerbation of CKD in patients with diabetes, and developing diagnostic and therapeutic drugs targeting such factors.
- 5) Pathophysiology of uremic toxins on organ crosstalk and impact of uremia management in CKD
- 6) Identifying a novel renoprotective mechanism based on the molecular inflammatory axis in

kidney injury

- 7) Pathophysiological role of organelle stress, organelle crosstalk damage in renal injury

Research Funds (PI)

- Japan Society for the Promotion of Science, Grants-in-Aid for Scientific Research
21H02824 (to **Reiko Inagi**, Novel tubular homeostasis mechanism mediated by primary cilia),
21K9439 (to **Reiko Inagi**, Pathophysiological role of organelle contact site in tubular homeostasis),
21K6159 (to **Sho Hasegawa**, Unraveling the role of ER-mitochondria crosstalk in the pathogenesis of diabetic kidney disease),
 • Japan Agency for Medical Research and Development (AMED)
CREST 20gm1410005s0101 (to **Reiko Inagi**, Study on understanding of the molecular mechanisms of tissue-specific unfolded protein responses for radical cure of human chronic diseases)

Awards

Prof. Reiko Inagi received the Kidney International Best Reviewers Award 2023.

References

1. Kawabata C, Hirakawa Y, Inagi R, Nangaku M. Acetate attenuates kidney fibrosis in an oxidative stress-dependent manner. *Physiol Rep*. 2023 Jul; 11(14):e15774. doi: 10.14814/phy2.15774. PMID: 37463875; PMCID: PMC10354006.
2. Nakamura Y, Matsumoto H, Wu CH, Fukaya D, Uni R, Hirakawa Y, Katagiri M, Yamada S, Ko T, Nomura S, Wada Y, Komuro I, Nangaku M, Inagi R, Inoue T. Alpha 7 nicotinic acetylcholine receptors signaling boosts cell-cell interactions in macrophages effecting anti-inflammatory and organ protection. *Commun Biol*. 2023 Jun 23; 6(1):666. doi: 10.1038/s42003-023-05051-2. PMID: 37353597; PMCID: PMC10290099.
3. Nangaku M, Kitching AR, Boor P, Fornoni A, Floege J, Coates PT, Himmelfarb J, Lennon R, Anders HJ, Humphreys BD, Caskey FJ, Fogo AB; TRANSFORM group. International Society of Nephrology first consensus guidance for

preclinical animal studies in translational nephrology. *Kidney Int.* 2023 Jul;104(1):36-45. doi: 10.1016/j.kint.2023.03.007. Epub 2023 Mar 28. Erratum in: *Kidney Int.* 2023 Oct;104(4):859. doi: 10.1016/j.kint.2023.08.001. PMID: 37001557.

4. Bravo-Sagua R, Lopez-Crisosto C, Criollo A, Inagi R, Lavandero S. Organelle Communication: Joined in Sickness and in Health. *Physiology (Bethesda)*. 2023 May 1;38(3):0. doi: 10.1152/physiol.00024.2022. PMID: 36856309.
5. Inagi R, Yoshioka K. Stray tubules: the varied and dynamic fate of tubular cells. *Kidney Int.* 2023 Jul;104(1):19-21. doi: 10.1016/j.kint.2023.02.005. Epub 2023 Feb 18. PMID: 36804410.
6. Inagi R, Hasegawa S. Good and evil, more reasons to study UPR. *Kidney Int.* 2023 Feb; 103(2):254-256. doi: 10.1016/j.kint.2022.09.015. PMID: 36681453.
7. Hasegawa S, Inagi R. Molecular mechanisms of kidney crosstalk with distant organs. *Nat Rev Nephrol.* 2023 Feb;19(2):75-76. doi: 10.1038/s41581-022-00655-z. PMID: 36434161.

Department of Retinal Biology and Pathology

Project Professor

Sumiko Watanabe, Ph.D.

Project Assistant Professor

Toshiro Iwagawa, Ph.D

※The following information is the same as that of the previous year for certain reasons.

Introduction and Organization

We are focusing on analysis of retinal development and basic mechanisms of retinal degenerative diseases with ultimate goal to elucidate new targets for drug design in ocular diseases. Faculties are Ph.D, basic medical scientists, and graduate students consist of both Ph.D type and MD background students. Our laboratory had been established 2021 July and is supported by Chugai-pharmaceutical co. The basis of our laboratory is Department of Molecular and Developmental Biology, which was in The Institute of Medical Science, University of Tokyo (IMSUT) until 2021. Major members of current laboratory including the faculties were working on molecular basis of retinal development especially focusing on transcriptional mechanisms including epigenetics of retinal development at this laboratory in IMSUT. Recent few years, we had focused on working on retinitis pigmentosa, which is the inherited severe retinal degenerative disease. Analysis of impact of the gene mutations, which was reported from patients genomic analysis, for maintenance of photoreceptor homeostasis was main strategy of our research. However, we had started analysis of roles of inflammation for onset and progression of retinal degeneration. Determination of the cells which contribute to build the inflammatory environment within retina is an important issue to be solved. There are several retinal immunocompetent cells, such as microglia, astrocyte, Mueller glia, and retinal pigment epithelium (RPE), and we have

particular interests with the microglia. After starting the new laboratory in the hospital, we expanded our focus from retina to retina and sclera with particular interest with blood vessels. Therefore, not only retinitis pigmentosa, various vessel related retinal diseases such as ocular complications of diabetic mellitus and aged macular degeneration (AMD) are our research targets. Microglia and inflammatory environment in retina may play pivotal roles for the vessel related retinal degenerative diseases, and we had established several assay systems related to this point both in in vitro and in vivo.

The laboratory also aims to bridge the basic research - and the clinical-team. We have regular discussion of our laboratory members and ophthalmology department clinicians, and exchange knowledge and techniques between two groups. By such efforts, we aim to establish basic/clinical collaborative research group in ophthalmology field.

Teaching activities

The graduate students (2 Ph.D candidates) are clinicians, and have their own project. In 2022, we published 2 papers of the students projects to scientific journals. Group data discussion, laboratory data discussion, journal club, and individual data discussion are regularly hold by onsite as well as online. One of our purposes to establish the lab here from IMSUT is to establish structure of mutual collaboration between clinicians and basic science researchers. For that

purpose, we have regular data conference between ophthalmology department and us, and faculties of both laboratories also have regular meeting to discuss project direction. We also participate to train Ph.D candidate students of the ophthalmology department by teaching principles of experimental techniques and discussing research data. Vice versa, we learnt how to do ophthalmology related several image analyses, such as OCT and fundus photography of the mouse. These techniques help us to expand choice of analyses of disease model mice. In addition, as a hub laboratory in the basic ophthalmology related works, students and young researchers in the University of Tokyo and other universities often visit us to learn techniques and knowledge in this field.

Research activities

Summary of the research: Retinal degeneration mice and human iPS cells are two major models used in our research, and several projects of the retina and cornea are ongoing. Technically, we employ molecular biology, biochemistry, electroretinogram, and several imaging analyses. In addition, the LC-MS based membrane lipid analysis and the proteome in collaboration with the experts are often used. Ophthalmological techniques also facilitate to make our research activities deepen with broad spectrum. We had focused on retinal neurons and microglia, but now include more posterior segment of the eye, such as RPE, choriocapillaris, and choroid. Details of some of specific projects are as follows.

*** Roles of CSF2 as a modulator of inflammation during retinal degeneration**

Colony-stimulating factor 2 (CSF2) is a potent cytokine that stimulates myeloid cells, such as dendritic cells and macrophages. We have been analyzing the roles of microglia in retinal degeneration through the modulation of inflammation in the eye, and examined the roles of CSF2 in this process. Transcripts of both subunits of the CSF2 receptor are expressed in microglia, but no evidence suggesting the involvement of CSF2 in inflammation in the degenerating eye has been reported. We found that *Csf2* transcripts were induced in the early phase of *in vitro* mouse adult retina culture, used as degeneration models, suggesting that

CSF2 induction is one of the earliest events occurring in the pathology of retinal degeneration. To examine the roles of CSF2 in retinal inflammation, we overexpressed CSF2 in retinal explants. Induction of CSF2 activated microglia and Müller glia, and the layer structure of the retina was severely perturbed. C-C motif chemokine ligand 2 (*Ccl2*) and C-X-C motif chemokine ligand 10 (*Cxcl10*), both of which are expressed in activated microglia, were strongly induced by the expression of CSF2 in the retina. However, addition of CSF2 to microglial cell lines MG5 and BV2 did not show apparent effects of CSF2 except weak induction of *Ccl2* transcripts and proliferation, suggesting that CSF2 induced strong inflammation in the context of the retinal environment, probably through editing molecular network of initial phase of degeneration.

***Downregulation of VEGF in the Retinal Pigment Epithelium Followed by Choriocapillaris Atrophy After NaIO3 Treatment in Mice**

Sodium iodate (NaIO3) induces retinal pigment epithelium (RPE) dysfunction, which leads to photoreceptor degeneration. This system is widely used as retinitis pigmentosa model. Previously, we used electron microscopy to show that the administration of NaIO3 resulted in the accumulation of cell debris in the subretinal space, which was thought to be caused by failed phagocytosis in the outer segment of the photoreceptor due to RPE dysfunction. We further analyzed the pathological changes in the retina and choroid of NaIO3-injected mice, and found that the expression of OTX2, an RPE marker, disappeared from central part of the RPE 1 day after NaIO3 administration. Furthermore, fenestrated capillaries (choriocapillaris, CC) adjacent to the RPE could not be identified only 2 days after NaIO3 administration. An examination of the expression of the CC-specific protein plasmalemma vesicle-associated protein (PLVAP), in sections and flat-mount retina/choroid specimens showed destruction of the CC, and complete disappearance of the PLVAP signal 7 days after NaIO3 administration. In contrast, CD31 flat-mount immunohistochemistry of the retina indicated no difference in retinal vessels between NaIO3-treated mice and controls. Electron microscopy showed that the fenestrated capillaries in the kidney and duodenum

were morphologically indistinguishable between control and NaIO₃-treated mice. We examined cytokine production in the retina and RPE, and found that the *Vegfa* transcript level in the RPE decreased starting 1 day after NaIO₃ administration. Taken together, these observations show that NaIO₃ reduces the CC in the early stages of the pathology, which is accompanied by a rapid decrease in *Vegfa* expression in the RPE.

A loss of the CC has been reported in various ocular degenerative diseases, mainly based on recent technical development of optical coherence tomography angiography (OCTA). CC flow alterations were shown to be associated with the development and progression of AMD, and retinitis pigmentosa. Our observation of the loss of the CC in the early phase of NaIO₃-induced pathogenesis may contribute to understanding of roles of alteration of CC in pathogenesis of the retinal degenerative diseases.

References

1. Azuma, K., Koumura, T., Iwamoto, R., Matsuoka, M., Terauchi, R., Yasuda, S., Shiraya, T., Watanabe, S., Aihara, M., Imai, H., Ueta, T., Mitochondrial GPx4 is indispensable for photoreceptor development and survival in mice, *JBC*, 2022, 298, 101824
2. Nagata, K., Hishikawa, D., Sagara, H., Saito, M., Watanabe, S., Shimizu, T., Shindou, H. Lysophosphatidylcholine acyltransferase 1 controls mitochondrial reactive oxygen species generation and survival of retinal photoreceptor cells, *JBC*, 2022, 298, 101958
3. Saita, K., Moriuchi, Y., Iwagawa, T., Aihara, M., Takai, Y., Uchida, K., Watanabe, S., Roles of CSF2 as a modulator of inflammation during retinal degeneration, *Cytokine*, 2022 158, 155996

Department of Real-world Evidence

Project Associate Professor

Yusuke Sasabuchi, M.D., M.P.H, Ph.D.

Project Lecturer

Shotaro Aso, M.D., M.P.H, Ph.D.

History and Overview of the Organization

Real-World Data (RWD) refers to patient data collected in daily clinical settings, distinct from the controlled environments of Randomized Controlled Trials (RCTs). This includes data from insurance databases, health check-ups, and electronic medical records. Evidence derived from RWD research is known as Real-World Evidence (RWE). RWD research is rapidly evolving globally. Regulatory authorities in Europe and America have opted to utilize RWE for expanding indications and safety monitoring of pharmaceuticals and medical devices. This has promoted an integrated approach to the utilization of RWD among industry, government, and academia.

In this context, the Department of Real-world Evidence was established in December 2022 as a social collaboration department with funding from DeSC Healthcare Corporation. The department aims to enhance public health and well-being by promoting multidisciplinary research using Japan's RWD to generate RWE and disseminating these findings to society. The collaborating department is the Department of Clinical Epidemiology & Economics (Professor Hideo Yasunaga).

The founding faculty members include Project Associate Professor Yusuke Sasabuchi (appointed December 2022) and Project Lecturer Shotaro Aso (appointed April 2023).

The creation of RWE can enhance daily clinical

practice through updated medical knowledge, improve the efficacy and safety of pharmaceuticals and medical devices, and contribute to their development. RWD research can fill gaps in evidence where RCTs are challenging to implement, thereby contributing to evidence-based medicine. It can also contribute to building a sustainable medical system through health economic policy research. Additionally, the department aims to reflect research outcomes in medical education and train data scientists.

Educations

The Department of Real-world Evidence provides support for lectures and guidance to students specializing in the School of Public Health at the collaborating Department of Clinical Epidemiology & Health Economics, as well as lectures and guidance for students in the Medical Real-World Data Utilization Personnel Training Program.

- For students specializing in the School of Public Health: Support is provided for Clinical Epidemiology & Health Economics exercises including a lecture in Clinical Epidemiology (1 session) by Sasabuchi.
- Sasabuchi and Aso provide guidance to students specializing in the School of Public Health.
- Medical Real-World Data Utilization Personnel Training Program: Introduction to Medical Real-World Data Construction (1 session) Clinical Issue Analysis and Practical

Management (4 sessions) Practical Task Training 2 (task presentation and evaluation) Guidance for specialized students: Sasabuchi, Aso

- In the Medical Real-World Data Utilization Personnel Training Program, the curriculum includes 'Introduction to Medical Real-World Data Construction' (1 session), 'Clinical Issue Analysis and Practical Management' (4 sessions), and 'Practical Task Training 2' (task presentation and evaluation), with Sasabuchi and Aso providing guidance to specialized students.

Research activities

Two faculty members from the Department of Real-world Evidence directly guide students and researchers in RWD research, thereby fostering their skills as data scientists. The department's research activities focus on pharmacological epidemiology, clinical epidemiology, and health economic policy research. This focus emphasizes utilizing RWD from various sources, including the DeSC database, the national database (NDB), the DPC database, patient registries, and electric medical records. Through these educational and research activities, the department aims to respond to the societal demand for RWD research and RWE utilization, promote research using Japan's RWD, and contribute to overall health improvement.

References

1. Murooka Y, Sasabuchi Y, Takazawa T, Matsui H, Yasunaga H, Saito S. Long-Term Prognosis Following Early Rehabilitation in the ICU: A Retrospective Cohort Study. *Crit Care Med*. 2023;51:1054-1063.
2. Iwasaki Y, Ohbe H, Nakajima M, Sasabuchi Y, Ikumi S, Kaiho Y, Yamauchi M, Fushimi K, Yasunaga H. Association Between Intraoperative Landiolol Use and In-Hospital Mortality After Coronary Artery Bypass Grafting: A Nationwide Observational Study in Japan. *Anesth Analg*. 2023;137:1208-1215.
3. Fukano K, Iizuka Y, Nishiyama S, Yoshinaga K, Uchino S, Sasabuchi Y, Sanui M. Characteristics of pulmonary artery catheter use in multicenter ICUs in Japan and the association with mortality: a multicenter cohort study using the Japanese Intensive Care PATient Database. *Crit Care*. 2023; 27:412.
4. Okada A, Honda A, Watanabe H, Sasabuchi Y, Aso S, Kurakawa KI, Nangaku M, Yamauchi T, Yasunaga H, Chikuda H, Kadowaki T, Yamaguchi S. Proteinuria screening and risk of bone fracture: a retrospective cohort study using a nationwide population-based database. *Clin Kidney J*. 2023;17:sfad302.
5. Kameda S, Sasabuchi Y, Michihata N, Yamana H, Matsui H, Fushimi K, Yasunaga H, Kohro T. Prednisolone versus cyclosporine as initial treatment for Kawasaki disease. *Pediatr Int*. 2023;65:e15658.
6. Ohbe H, Ouchi K, Miyamoto Y, Ishigami Y, Matsui H, Yasunaga H, Sasabuchi Y. One-Year Functional Outcomes After Invasive Mechanical Ventilation for Older Adults With Preexisting Long-Term Care-Needs. *Crit Care Med*. 2023;51: 584-593.
7. Ohbe H, Nakajima M, Miyamoto Y, Shibahashi K, Matsui H, Yasunaga H, Sasabuchi Y. 1-year functional outcomes after cardiopulmonary resuscitation for older adults with pre-existing long-term care needs. *Age Ageing*. 2023;52: afad072.
8. Ohbe H, Sasabuchi Y, Doi K, Matsui H, Yasunaga H. Association Between Levels of Intensive Care and In-Hospital Mortality in Patients Hospitalized for Sepsis Stratified by Sequential Organ Failure Assessment Scores. *Crit Care Med*. 2023;51:1138-1147.
9. Nishimoto Y, Ohbe H, Matsui H, Nakata J, Takiguchi T, Nakajima M, Sasabuchi Y, Sato Y, Watanabe T, Yamada T, Fukunami M, Yasunaga H. Trends in Mechanical Circulatory Support Use and Outcomes of Patients With Cardiogenic Shock in Japan, 2010 to 2020. *Am J Cardiol*. 2023;203:203-211.
10. Nishimoto Y, Ohbe H, Matsui H, Nakajima M, Sasabuchi Y, Sato Y, Watanabe T, Yamada T, Fukunami M, Yasunaga H. Trends in Treatment Patterns and Outcomes of Patients With Pulmonary Embolism in Japan, 2010 to 2020. *J*

- Am Heart Assoc. 2023;12:e028981.
11. Suzuki R, Uchino S, Sasabuchi Y, Kawarai Lefor A, Shiotsuka J, Sanui M. Enteral free water vs. parenteral dextrose 5% in water for the treatment of hypernatremia in the intensive care unit: a retrospective cohort study from a mixed ICU. *J Anesth.* 2023;37:868-879.
 12. Hayashi K, Sasabuchi Y, Matsui H, Nakajima M, Ohbe H, Fushimi K, Ono K, Yasunaga H. Additive effectiveness of acrylonitrile-co-methallyl sulfonate surface-treated membranes in the treatment of pneumonia: A propensity score-matched retrospective cohort study. *Artif Organs.* 2023;47:408-416.
 13. Ohbe H, Sasabuchi Y, Iwagami M, Ogura T, Ono S, Matsui H, Yasunaga H. Intensive Care Unit versus High-dependency Care Unit for COVID-19 Patients with Invasive Mechanical Ventilation. *Ann Am Thorac Soc.* 2023;20:102-109.
 14. Hayashi K, Sasabuchi Y, Matsui H, Nakajima M, Otawara M, Ohbe H, Fushimi K, Ono K, Yasunaga H. Does early excision or skin grafting of severe burns improve prognosis? A retrospective cohort study. *Burns.* 2023;49:554-561.
 15. Ichita C, Nakajima M, Ohbe H, Kaszynski RH, Sasaki A, Miyamoto Y, Kondo Y, Sasabuchi Y, Fushimi K, Matsui H, Yasunaga H. Effectiveness of early colonoscopy in patients with colonic diverticular hemorrhage: Nationwide inpatient analysis in Japan. *Dig Endosc.* 2023;35:520-528.
 16. Ono S, Sasabuchi Y, Ishimaru M, Ono Y, Matsui H, Yasunaga H. Short-term effects of reduced cost sharing on childhood dental care utilization and dental caries prevention in Japan. *Community Dent Oral Epidemiol.* 2023;51:228-235.
 17. Shinmoto K, Ohbe H, Nakajima M, Miyamoto Y, Sasabuchi Y, Yasunaga H, Hiraoka E. Outcomes after early versus delayed antibiotic treatment of liver abscess in Japan: A nationwide retrospective cohort study. *J Infect Chemother.* 2023;29:1-6.
 18. Wada Y, Takahashi H, Sasabuchi Y, Usui R, Ogoyama M, Suzuki H, Ohkuchi A, Fujiwara H. Maternal outcomes of placental abruption with intrauterine fetal death and delivery routes: A nationwide observational study. *Acta Obstet Gynecol Scand.* 2023;102:708-715.
 19. Watanabe J, Sasabuchi Y, Ohbe H, Nakajima M, Matsui H, Miki A, Horie H, Kotani K, Yasunaga H, Sata N. Impact of Preoperative Stoma Site Marking on Morbidity and Mortality in Patients with Colorectal Perforation: A Nationwide Retrospective Cohort Study. *World J Surg.* 2023; 47:2857-2864.
 20. Kamei J, Sugihara T, Yasunaga H, Matsui H, Sasabuchi Y, Fujimura T, Homma Y, Kume H. Impact of early ureteral drainage on mortality in obstructive pyelonephritis with urolithiasis: an analysis of the Japanese National Database. *World J Urol.* 2023;41:1365-1371.
 21. Nishimoto Y, Ohbe H, Matsui H, Nakajima M, Sasabuchi Y, Sato Y, Watanabe T, Yamada T, Fukunami M, Yasunaga H. Effectiveness of systemic thrombolysis on clinical outcomes in high-risk pulmonary embolism patients with venoarterial extracorporeal membrane oxygenation: a nationwide inpatient database study. *J Intensive Care.* 2023;11:4.
 22. Konishi T, Sasabuchi Y, Matsui H, Tanabe M, Seto Y, Yasunaga H. Long-Term Risk of Being Bedridden in Elderly Patients Who Underwent Oncologic Surgery: A Retrospective Study Using a Japanese Claims Database. *Ann Surg Oncol.* 2023;30:4604-4612.
 23. Kasuya S, Aso S, Takahashi I. Effects of shorter activated coagulation time on hemorrhage during venoarterial extracorporeal membrane oxygenation. *Ann Clin Epidemiol.* 2023;5:74-79.
 24. Tanaka C, Tagami T, Nakayama F, Kuno M, Kitamura N, Yasunaga H, Aso S, Takeda M, Unemoto K. Changes Over 7 Years in Temperature Control Treatment and Outcomes After Out-of-Hospital Cardiac Arrest: A Japanese, Multicenter Cohort Study. *Ther Hypothermia Temp Manag.* 2024;5:102-109.
 25. Aoki M, Aso S, Suzuki M, Tagami T, Sawada Y, Yasunaga H, Kitamura N, Oshima K. Association between obesity and neurological outcomes among out-of-hospital cardiac arrest patients: The SOS-KANTO 2017 study. *Resusc Plus.* 2023;17: 100513.
 26. Kishihara Y, Kashiura M, Yasuda H, Kitamura N, Nomura T, Tagami T, Yasunaga H, Aso S, Takeda M, Moriya T. Association between institutional volume of out-of-hospital cardiac arrest cases and

- short-term outcomes. *Am J Emerg Med*. 2024;75: 65-71.
27. Hattori Y, Tahara S, Aso S, Makito K, Matsui H, Fushimi K, Yasunaga H, Morita A. Comparison of prophylactic antibiotics for endonasal trans-sphenoidal surgery using a national inpatient database in Japan. *J Antimicrob Chemother*. 2023;78:2909-2914.
 28. Suzuki T, Taniguchi Y, Komiyama J, Kuno T, Adomi M, Abe T, Inokuchi R, Miyawaki A, Imai S, Saito M, Ohbe H, Aso S, Kamio T, Tamiya N, Iwagami M. Characteristics and in-hospital mortality of patients with COVID-19 from the first to fifth waves of the pandemic in 2020 and 2021 in the Japanese Medical Data Vision database. *Heliyon*. 2023;9:e19490.
 29. Tahara S, Hattori Y, Aso S, Uda K, Kumazawa R, Matsui H, Fushimi K, Yasunaga H, Morita A. Endoscopic surgery versus craniotomy for spontaneous intracerebral hemorrhage in the late elderly patients. *J Stroke Cerebrovasc Dis*. 2023; 32:107327.
 30. Yamamoto R, Tamura T, Haiden A, Yoshizawa J, Homma K, Kitamura N, Sugiyama K, Tagami T, Yasunaga H, Aso S, Takeda M, Sasaki J. Frailty and Neurologic Outcomes of Patients Resuscitated From Nontraumatic Out-of-Hospital Cardiac Arrest: A Prospective Observational Study. *Ann Emerg Med*. 2023;82:84-93.
 31. Aso S, Ono S, Michihata N, Uemura K, Yasunaga H. Effectiveness of vaccination on influenza-related critical illnesses in the elderly population. *J Infect Chemother*. 2023;29:576-579.
 32. Okada A, Kurakawa KI, Harita Y, Shimizu A, Yamaguchi S, Aso S, Ono S, Hashimoto Y, Kumazawa R, Michihata N, Jo T, Matsui H, Fushimi K, Nangaku M, Yamauchi T, Yasunaga H, Kadowaki T. Comparison of bleeding complications after pediatric kidney biopsy between intravenous sedation and general anesthesia: a nationwide cohort study. *BMC Pediatr*. 2023;23: 33.
 33. Tahara S, Hattori Y, Aso S, Uda K, Kumazawa R, Matsui H, Fushimi K, Yasunaga H, Morita A. Outcomes After Endoscopic Evacuation Versus Evacuation Using Craniotomy or Stereotactic Aspiration for Spontaneous Intracerebral Hemorrhage: Analysis Using a Japanese Nationwide Database. *Neurocrit Care*. 2023;38: 667-675.
 34. Hashimoto Y, Kaneko H, Aso S, Okada A, Matsui H, Yasunaga H, Aihara M, Obata R. Association between retinal vein occlusion and early-stage hypertension: A propensity score analysis using a large claims database. *Eye (Lond)*. 2023;37: 1741-1747.

Department of Lipidomics

Professor

Yoshiya Oda, Ph.D.

Assistant Professor

Suzumi M Tokuoka, Ph.D.

Homepage <http://lipidomics.m.u-tokyo.ac.jp/index-e.html>

Introduction and Organization

The Department of Lipidomics was established in April 2011, funded by Shimadzu Corp. and Ono Pharmaceutical Co., Ltd. The objective of the laboratory is to establish and improve mass spectrometry-based lipidomics methodologies, and its application to biomedical studies including basic lipid biology as well as clinical research.

The laboratory was started with three staff scientists, Takao Shimizu (Professor), Yoshihiro Kita (Associate Professor. He moved to Life Science Core Facility in Dec. 2013), and Suzumi Tokuoka (Assistant Professor). In April, 2014, Fuyuki Tokumasu joined as an Associate Professor (he moved to Nagasaki University in April, 2019) and in May 2018, Yoshiya Oda joined as a professor. In 2021, we have three guest researchers and two technical assistants. The department has been in existence for more than 20 years since the previous Metabolome department, which was founded in 2003.

Teaching activities

The department staffs gave several lectures for undergraduate and graduate students. For undergraduate students, Drs. Shimizu and Kita delivered several lectures on biochemistry. Dr. Kita gave lectures on “Proteome and metabolome” for master’s students and “Principles and Applications of Mass Spectrometry” for doctoral students.

Research activities

Our research interests cover following topics.

Methods for clinical samples

Studies using human specimens are more reflective of human diseases than experimental data using laboratory animals and cell lines. However, lipidomics analysis on human clinical specimens such as blood, urine, feces, and biopsy samples is not always optimized for lipidomics analysis because of the large variability of data depending on individual differences compared to animal experiments. We are developing a technique for handling clinical samples for lipidomics analysis, and are working to create a highly practical lipidomics analysis method. Furthermore, in the clinical field, it is required to measure a large number of samples to take into account individual differences. Therefore, we are developing high-throughput and highly reliable assays and applying them to clinical practice.

Lipid biomarker discovery

Lipid biomarker discovery by liquid chromatography-mass spectrometry-based method requires a high-level integration of chromatography and mass spectrometry, which ensures lipid separation, semi-quantitative detection, and identification. We are collaborating with industries to overcome known difficulties in lipid chromatography, develop differential analyses and feature-extraction methods, and establish an intelligent analytical system linked with lipid database.

Metabolic flux analysis of lipids

A simple lipidomics analysis provides large datasets

that describe the amount-based profile of lipidome. However, such a ‘snapshot’ analysis is not sufficient to understand the dynamics of lipid metabolic pathway, because changes in metabolic flux is not always reflected to static amount of metabolites. To overcome this situation, we are developing a flux-oriented lipidomics analysis using stable-isotope tracers.

Multiplex quantitation strategy for biologically active lipids

Lipid mediators, including prostaglandins, leukotrienes, platelet-activating factor, bile acids and many other bioactive lipid metabolites are attracting great attention as disease-related or physiologically important molecules. Comprehensive analysis of known lipids is a useful, unbiased method in disease mechanism studies, and the lipid profile is a useful parameter that characterizes disease status as well. We have developed an original multiplex quantification method for trace amounts of biologically active lipids using liquid chromatography-tandem mass spectrometry (LC-MS/MS). We are developing more sensitive and rapid methods that cover more lipid mediators, which meet the demands on various large-scale studies and high-throughput screening approaches.

Discovery of novel lipids and their related molecules metabolizing pathways

Although major biosynthetic and catabolic pathways for classical lipid mediators have been well documented so far, there are still possibilities for yet unidentified lipid mediator metabolizing pathways in vivo. We have obtained preliminary data for novel lipid mediator-producing pathway using gene-deficient mice. Using the latest lipidomics techniques to the cell cultures and animal models, we will elucidate a novel lipid mediator related pathway and its biological significance.

Expansion of proteomics based on immune-PCR

Until now, proteomics based on mass spectrometry has been the mainstream method, but quantitative analysis was poor and plasma proteomics could not detect proteins such as cytokines, which are only present in very small amounts. This is why we introduced this method for the first time in Japan. We have already found interesting biomarker candidates

in various diseases. We are also trying to integrate lipidomics and proteomics.

Automating Metabolite Analysis and Improving Coverage

Various methods are used to improve the coverage of metabolomics and lipidomics. One such method is gas chromatography (GC), which requires derivatization of the molecule to be analyzed. We are developing protocols to enable various derivatization methods using an automated derivatization system. Although individual molecules cannot be identified, we are investigating the possibility of risk diagnosis based on the profiles of blood components using a Fourier transform infrared spectrophotometer, which is fast, reproducible, and easy to operate. Our goal is to contribute to medical care by incorporating various technologies without limiting measurement methods.

References

1. Tokuoka SM, Hamano F, Kobayashi A, Adachi S, Andou T, Natsume T, Oda Y.. Plasma proteomics and lipidomics facilitate elucidation of the link between Alzheimer's disease development and vessel wall fragility, *Sci Rep.* 2024 Aug 27;14(1):19901.
2. Taketomi Y, Higashi T, Kano K, Miki Y, Mochizuki C, oyoshima S, Okayama Y, Nishito Y, Nakae S, Tanaka S, Tokuoka SM, Oda Y, Shichino S, Ueha S, Matsushima K, Akahoshi N, Ishii S, Chun J, Aoki J, Murakami M. Lipid-orchestrated paracrine circuit coordinates mast cell maturation and anaphylaxis through functional interaction with fibroblasts, *Immunity.* 2024 Aug 13;57(8):1828-1847.e11.
3. Hosoi T, Yakabe M, Sasakawa H, Sasako T, Ueki K, Kato S, Tokuoka SM, Oda Y, Abe M, Matsumoto T, Akishita M, Ogawa S. Sarcopenia phenotype and impaired muscle function in male mice with fast-twitch muscle-specific knockout of the androgen receptor. *Proc Natl Acad Sci U S A.* 2023 Jan 24; 120(4):e2218032120.
4. Kita Y, Tokuoka SM, Oda Y, Shimizu T. TRACES: A lightweight browser for liquid chromatography–multiple reaction monitoring–mass spectrometry chromatograms. *Metabolites*, 12, 354 (2022) (Published: 15 April 2022).

5. Tokuoka SM, Kita Y, Sato M, Shimizu T, Yatomi Y, Oda Y. Lipid profiles of human serum fractions enhanced with CD9 antibody-immobilized magnetic beads. *Metabolites*, 12, 230 (2022) (Published: 5 March 2022).
6. Hamano F, Tokuoka SM, Ishibashi M, Yokoi Y, Tourlousse DM, Kita Y, Sekiguchi Y, Yasui H, Shimizu T, Oda Y. Multi-omics analysis to generate hypotheses for mild health problems in monkeys. *Metabolites*, 11, 701 (2021) (Published: 13 October 2021).
7. Tokuoka SM, Kita Y, Sato M, Shimizu T, Yatomi Y, Oda Y. Development of Tandem Mass Tag Labeling Method for Lipid Molecules Containing Carboxy and Phosphate Groups, and Their Stability in Human Serum. *Metabolites*. 2020 Dec 30;11(1):19.
8. Tokuoka SM, Yasumoto A, Kita Y, Shimizu T, Yatomi Y, Oda Y. Limitations of deuterium-labeled internal standards for quantitative electrospray ionization mass spectrometry analysis of fatty acid metabolites. *Rapid Commun Mass Spectrom*. 2020 Jul 15;34(13):e8814.
9. Tokuoka SM, Kita Y, Shimizu T, Oda Y. Isobaric mass tagging and triple quadrupole mass spectrometry to determine lipid biomarker candidates for Alzheimer's disease. *PLoS One*. 2019 Dec 10; 14(12):e0226073.
10. Izumi Y, Matsuda F, Hirayama A, Ikeda K, Kita Y, Horie K, Saigusa D, Saito K, Sawada Y, Nakanishi H, Okahashi N, Takahashi M, Nakao M, Hata K, Hoshi Y, Morihara M, Tanabe K, Bamba T, Oda Y. Inter-Laboratory Comparison of Metabolite Measurements for Metabolomics Data Integration. *Metabolites*, 9, 257 (2019) (Published Online:31 October 2019)
11. Tanaka TQ, Tokuoka SM, Nakatani D, Hamano F, Kawazu S, Wellems TE, Kita K, Shimizu T, Tokumasu F. Polyunsaturated fatty acids promote *Plasmodium falciparum* gametocytogenesis. *Biol. Open*, 8, bio042259 (2019) (Published Online:20 June 2019)
12. Kohira T, Kita Y, Tokuoka SM, Shiba M, Satake M, Shimizu T. Characterization of supported liquid extraction as a sample pretreatment method for eicosanoids and related metabolites in biological fluids. *J Chrom B*, 1124, 298-307 (2019) (Published Online:12 Jun 2019)
13. Yoshida K, Kita Y, Tokuoka SM, Hamano F, Yamazaki M, Sakimura K, Kano M, Shimizu T. Monoacylglycerol lipase deficiency affects diet-induced obesity, fat absorption, and feeding behavior in CB1 cannabinoid receptor-deficient mice. *FASEB J*, 33, 2484-2497 (2019) (Published Online:30 Jan 2019)
14. Yanagida K, Igarashi H, Yasuda D, Kobayashi D, Ohto-Nakanishi T, Akahoshi N, Sekiba A, Toyoda T, Ishijima T, Nakai Y, Shojima N, Kubota N, Abe K, Kadowaki T, Ishii S, Shimizu T. The $G\alpha_{12/13}$ -coupled receptor, LPA4 limits proper adipose tissue expansion and remodeling in diet-induced obesity. *JCI Insight*, 3, e97293 (2018) (First published December 20, 2018)
15. Kita Y, Shiudou H, Shimizu T. Cytosolic phospholipase A2 and lysophospholipid acyl-transferases. *Biochim Biophys Acta*, 1864, 838-845 (2019) (Available online 9 August 2018)

Department of Preventive Medicine for Locomotive Organ Disorders

Project Professor

Noriko Yoshimura, M.D., Ph.D.

Project Research Associate

Toshiko Iidaka, M.D., Ph.D.

Homepage [http:// www.h.u-tokyo.ac.jp/research/center22/index.html](http://www.h.u-tokyo.ac.jp/research/center22/index.html)

Introduction and Organization

The department of Preventive Medicine for Locomotive Organ Disorders in 22nd Century Medical and Research Center, The University of Tokyo Hospital, on April 1st, 2023, which is a social collaboration department with Suntory Wellness Ltd., KYOCERA Corporation, ASAHI KASEI PHARMA CORPORATION and Fujifilm Corporation, and in close collaboration with departments of Orthopaedic Surgery and Rehabilitation Medicine in the hospital. Our department has been established to clarify the epidemiological profiles of locomotive organ disorders, such as, osteoarthritis (OA), osteoporosis (OP) and sarcopenia (SP). Further, we also try to elucidate the frequencied and risk factors for locomotive syndrome, which was defined by the Japanese Orthopaedic Association (JOA) in 2014.

Research activities

Although locomotive organ disorders are major causes of disability and require support, little information is available regarding their epidemiology. The Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) study, which started in 2005-7, is a prospective cohort study that aims to elucidate the environmental and genetic background for bone and joint diseases. It was designed to examine the extent to which risk factors for these diseases are related to clinical features, laboratory and radiographic findings, bone mass and geometry, lifestyle, nutritional factors,

anthropometric and neuromuscular measures, and fall propensity. In addition, the study's aim was also to determine how these diseases affect activities of daily living and quality of life in Japanese men and women.

We completed the baseline study in 2005-2007, then, 2nd, 3rd, 4th, and 5th follow-ups were completed in 2008-2010, 2012-2013, 2015-2016, 2018-2019, 2022-2023, respectively. We have been conducting follow-up surveys.

References

1. Takeda R, Mizuhara H, Uchio A, Iidaka T, Makabe K, Kasai T, Omata Y, Yoshimura N, Tanaka S, Matsumoto T: Automatic estimation of hallux valgus angle using deep neural network with axis-based annotation. *Skeletal Radiol* 53(11): 2357-2366, 2024, doi: 10.1007/s00256-024-04618-2.
2. Teraguchi M, Hashizume H, Asai Y, Oka H, Nagata K, Ishimoto Y, Iwasaki H, Tsutsui S, Takami M, Tanaka S, Yoshida M, Yoshimura N, Yamada: Association between modic changes, disc degeneration, and pelvic incidence-lumbar lordosis mismatch in a large opulation based cohort: the Wakayama spine study. *Eur Spine J*, 2023 Apr 26, online, doi: 10.1007/s00586-023-07702-8.
3. Teraguchi M, Hashizume H, Oka H, Kagotani R, Nagata K, Ishimoto Y, Tanaka S, Yoshida M, Yoshimura N, Yamada H: Prevalence and

- distribution of Schmorl node and endplate signal change, and correlation with disc degeneration in a population-based cohort: the Wakayama Spine Study. *Eur Spine J* 33(1): 103-110, 2024, doi: 10.1007/s00586-023-08009-4.
4. Vandenput L, Johansson H, McCloskey EV, Liu E, Schini M, Åkesson KE, Anderson FA, Azagra R, Bager CL, Beaudart C, Bischoff-Ferrari HA, Biver E, Bruyère O, Cauley JA, Center JR, Chapurlat R, Christiansen C, Cooper C, Crandall CJ, Cummings SR, Da Silva JA, Dawson-Hughes B, Diez-Perez A, Dufour AB, Eisman JA, Elders PJ, Ferrari S, Fujita Y, Fujiwara S, Glüer CC, Goldshtein I, Goltzman D, Gudnason V, Hall J, Hans D, Hoff M, Hollick RJ, Huisman M, Iki M, Ish-Shalom S, Jones G, Karlsson MK, Khosla S, Kiel DP, Koh WP, Koromani F, Kotowicz MA, Kröger H, Kwok T, Lamy O, Langhammer A, Larijani B, Lippuner K, Mellström D, Merlijn T, Nguyen TV, Nordström A, Nordström P, O'Neill TW, Obermayer-Pietsch B, Ohlsson C, Orwoll ES, Pasco JA, Rivadeneira F, Schott AM, Shiroma EJ, Siggeirsdottir K, Eleanor M Simonsick EM, Sornay-Rendu E, Sund R, Swart KM, Szulc P, Tamaki J, Torgerson DJ, van Schoor NM, van Staa TP, Vila J, Wareham NJ, Wright NC, Yoshimura N, Zillikens MC, Zwart M, Harvey NC, Lorentzon M, Leslie WD, Kanis JA: A meta-analysis of previous falls and subsequent fracture risk. *Osteoporos Int* 35(3): 469-494, 2024, doi:10.1007/s00198-023-07012-1.
 5. Tomomatsu K, Taniguchi T, Hashizume H, Harada T, Iidaka T, Asai Y, Oka H, Shigeyuki Muraki S, Akune T, Kawaguchi H, Nakamura K, Yoshida M, Tanaka S, Yoshimura N, Yamada H: Factors associated with cam deformity in Japanese local residents. *Sci Rep* 14(1): 1585, 2024, doi: 10.1038/s41598-024-51876-0.
 6. Kitamura B, Iidaka T, Horii C, Muraki S, Oka H, Kawaguchi H, Nakamura K, Akune T, Otsuka Y, Izumo T, Tanaka T, Rogi T, Shibata H, Tanaka S, Yoshimura N: Ten-year trends in values of joint space width and osteophyte area of knee joints: Comparison of the baseline and fourth ROAD study surveys. *Osteoarthr Cartil Open* 6(2): 100454, 2024, doi:10.1016/j.ocarto.2024.100454.
 7. Taniguchi Y, Akune T, Nishida N, Omori G, Kim HA, Ueno K, Saito T, Oichi T, Koike A, Mabuchi A, Oka H, Muraki S, Oshima Y, Kawaguchi H, Nakamura K, Tokunaga K, Tanaka S, Yoshimura N: A common variant rs2054564 in ADAMST17 is associated with susceptibility to lumbar 3 spondylosis. *Scientific Reports* 13 (1): 4900, 2023. doi: 10.1038/s41598-023-32155-w.
 8. Nagata K, Hashizume H, Oka H, Ishimoto Y, Muraki S, Nakamura K, Yoshida M, Tanaka S, Yamada H, Yoshimura N: Plasma pentosidine concentration is associated with ligament ossification and high-grade osteoarthritis: The ROAD study. *Geriatr Gerontol Int* 24(1): 154-160, 2024, doi: 10.1111/ggi.14745.
 9. Westbury LD, Fuggle NR, Pereira D, Oka H, Yoshimura N, Oe N, Mahmoodi S, Niranjana M, Dennison EM, Cooper C: Machine learning as an adjunct to expert observation in classification of radiographic knee osteoarthritis: findings from the Hertfordshire Cohort study. *Aging Clin Exp Res* 35(7): 1449-1457, 2023 doi: 10.1007/s40520-023-02428-5.
 10. Inoue I, Yoshimura N, Iidaka T, Horii C, Muraki S, Oka H, Kawaguchi H, Akune T, Maekita T, Mure K, Nakamura K, Tanaka S, Ichinose M: Trends in the prevalence of atrophic gastritis and *Helicobacter pylori* infection over a 10-year period in Japan: The ROAD study 2005-2015. *Mol Clin Oncol* 19(1): 53, 2023, doi: 10.3892/mco.2023.2649.
 11. Higuchi J, Matsumoto T, Kasai T, Takeda R, Iidaka T, Horii C, Oka H, Muraki S, Hashizume H, Yamada H, Yoshida M, Nakamura K, Tanaka S, Yoshimura N: Relationship between medial hallux sesamoid and hallux valgus in the general population. *Foot Ankle Surg* 29(8): 621-626, 2023, doi: 10.1016/j.fas.2023.07.011.
 12. Murata S, Hashizume H, Tsutsui S, Oka H, Teraguchi M, Ishimoto Y, Nagata K, Takami M, Iwasaki H, Minamide A, Nakagawa Y, Tanaka S, Yoshimura N, Yoshida M, Yamada H: Publisher Correction: Pelvic compensation accompanying spinal malalignment and back pain-related factors in a general population: the Wakayama spine study. *Sci Rep* 13(1): 12791, 2023, doi: 10.1038/s41598-023-39895-9. Erratum for: *Sci Rep*. 2023 Jul 22;13(1):11862.

13. Dennison EM, Laskou F, Westbury LD, Bevilacqua G, Fuggle NR, Iidaka T, Horii C, Tanaka S, Yoshimura N, Cooper C: Do lifestyle, anthropometric and demographic factors associated with muscle strength differ in a UK and Japanese cohort? An exploratory analysis. *Aging Clin Exp Res* 35(12): 3097-3104, 2023, doi: 10.1007/s40520-023-02614-5.
14. Kanis JA, Johansson H, McCloskey EV, Liu E, Åkesson KE, Anderson FA, Azagra R, Bager CL, Beaudart C, Bischoff-Ferrari HA, Biver E, Bruyère O, Cauley JA, Center JR, Chapurlat R, Christiansen C, Cooper C, Crandall CJ, Cummings SR, da Silva JAP, Dawson-Hughes B, Diez-Perez A, Dufour AB, Eisman JA, Elders PJM, Ferrari S, Fujita Y, Fujiwara S, Glüer CC, Goldshtein I, Goltzman D, Gudnason V, Hall J, Hans D, Hoff M, Hollick RJ, Huisman M, Iki M, Ish-Shalom S, Jones G, Karlsson MK, Khosla S, Kiel DP, Koh WP, Koromani F, Kotowicz MA, Kröger H, Kwok T, Lamy O, Langhammer A, Larijani B, Lippuner K, Mellström D, Merlijn T, Nordström A, Nordström P, O'Neill TW, Obermayer-Pietsch B, Ohlsson C, Orwoll ES, Pasco JA, Rivadeneira F, Schott AM, Shiroma EJ, Siggeirsdottir K, Simonsick EM, Sornay-Rendu E, Sund R, Swart KMA, Szulc P, Tamaki J, Torgerson DJ, van Schoor NM, van Staa TP, Vila J, Wareham NJ, Wright NC, Yoshimura N, Zillikens MC, Zwart M, Vandenput L, Harvey NC, Lorentzon M, Leslie WD. Previous fracture and subsequent fracture risk: a meta-analysis to update FRAX. *Osteoporos Int* 34(12): 2027-2045, 2023, doi: 10.1007/s00198-023-06870-z.

University Hospital

Clinical Services

Advanced Medical Center for Heart Failure

Director, Associate Professor

Masaru Hatano, M.D., Ph.D.

Vice Director

Masahiko Ando, M.D., Ph.D.

※The following information is the same as that of the previous year for certain reasons.

Homepage <https://www.h.u-tokyo.ac.jp/patient/depts/shinfuzen/>

Introduction and Organization

Advanced medical center for heart failure collaborates with a wide range of university hospitals and core regional medical institutions to accept patients who require heart transplantations of ventricular assist device (VAD) implantation. In addition to cardiovascular medicine and cardiovascular surgery, the center provides medical care with a heart team consisting of recipient transplant coordinators, pharmacists, medical engineers and physical therapists. In addition to such medical cooperation efforts, the center is also responsible for training heart failure specialists and other specialized staff by accepting trainees.

failure condition. It is also recognized as a facility that can perform destination therapy.

- Drug therapy for heart failure: The center has extensive experience in the use of heart failure drugs, including those that have been in recent years.
- Introduction of Vyndaqel for cardiac amyloidosis: The center has been certified to prescribe Vyndaqel by The Japanese Circulation Society and have already gained a significant amount of experience with the drug.
- HeartSeet: The center participates in a post-marketing clinical trial of HeartSeet, a skeletal myoblast sheet to be transplanted onto the surface of the heart.

Clinical activities

Target diseases include idiopathic cardiomyopathies such as dilated cardiomyopathy and hypertrophic cardiomyopathy, various types of secondary cardiomyopathy, and all causes of heart failure regardless of underlying disease

- Heart transplantation : Performed 213
Heart transplantation to date (as of 25 Dec 2023), the largest number in Japan
- Ventricular Assist Device (VAD): The center can employ all types of VADs approved in Japan, making it possible to choose the most suitable model according to each patient's physical and heart

Teaching and Research activities

In addition to medical care, we accept training in advanced heart failure management from medical facilities nationwide and play an important role in training heart failure specialists and specialized staff. We are also focusing on research and in addition to disseminating many research results, we are promoting translational research that bridges basic research and clinical practice. In addition, while treating a large number of heart failure patients, we are also striving to establish optimal prevention and treatment strategy (precision medicine) that consider individual differences.

References

1. Fujiwara T, Takeda N, Hara H, Ishii S, Numata G, Tokiwa H, Katoh M, Maemura S, Suzuki T, Takiguchi H, Yanase T, Kubota Y, Nomura S, Hatano M, Ueda K, Harada M, Toko H, Takimoto E, Akazawa H, Morita H, Nishimura S, Komuro I. PGC-1 α -mediated angiogenesis prevents pulmonary hypertension in mice. *JCI Insight*. 2023 Sep 8;8(17):e162632.
2. Isotani Y, Amiya E, Hatano M, Kiriyaama H, Uehara M, Ishida J, Tsuji M, Bujo C, Narita K, Ishii S, Kakuda N, Minatsuki S, Yagi H, Saito A, Numata G, Yamada T, Kurihara T, Suzuki T, Komuro I. A new assessment method for right ventricular diastolic function using right heart catheterization by pressure-volume loop. *Physiol Rep*. 2023 Jul;11(13):e15751.
3. Minatsuki S, Hatano M, Tanikawa I, Hirose K, Saito A, Yagi H, Takeda N, Komuro I. Verification of Optimal Balloon Size in Balloon Pulmonary Angioplasty for Chronic Thromboembolic Pulmonary Hypertension. *Cardiovasc Intervent Radiol*. 2023 Jul;46(7):967-969.
4. Kiriyaama H, Kiyosue A, Minatsuki S, Kawahara T, Katsushika S, Kamon T, Hirose K, Shinohara H, Miura M, Saito A, Kikuchi H, Koder S, Hatano M, Ando J, Myojo M, Itoh N, Yamamoto K, Ikenouchi H, Takeda N, Komuro I. Potential value of saline-induced Pd/Pa ratio in patients with coronary artery stenosis. *Front Cardiovasc Med*. 2023 Jan 6;9:1001833.
5. Ishii S, Hatano M, Maki H, Minatsuki S, Saito A, Yagi H, Shimbo M, Soma K, Numata G, Fujiwara T, Takeda N, Komuro I. Prognostic value of follow-up vasoreactivity test in pulmonary arterial hypertension. *J Cardiol*. 2023 Jul;82(1):69-75.
6. Yamada T, Nomura S, Amiya E, Katoh M, Inoue S, Hatsuse S, Fujita K, Ito M, Fujita T, Bujo C, Tsuji M, Ishida J, Ko T, Yamada S, Katagiri M, Sassa T, Kinoshita O, Nawata K, Tobita T, Satoh M, Ishiwata J, Daimon M, Tatsuno K, Fukuda S, Kashimura T, Minamino T, Hatano M, Ono M, Aburatani H, Komuro I. LMNA Mutations and Right Heart Failure in Patients With Cardiomyopathy and With Left Ventricular Assist Devices. *J Card Fail*. 2023 May;29(5):855-857.
7. Atsukawa M, Tsubota A, Kondo C, Koyano KS, Ishikawa T, Toyoda H, Takaguchi K, Watanabe T, Matsuura K, Ogawa C, Hiraoka A, Okubo H, Tateyama M, Uojima H, Nozaki A, Chuma M, Kato K, Mikami S, Tani J, Morishita A, Kawata K, Tada T, Furuichi Y, Okubo T, Kawano T, Arai T, Kawabe N, Kawamura N, Ikegami T, Nakamuta M, Shigefuku R, Iwasa M, Tanaka Y, Hatano M, Iwakiri K. Risk factors for portopulmonary hypertension in patients with cirrhosis: a prospective, multicenter study. *Hepatol Int*. 2023 Feb;17(1):139-149.
8. Dai Z, Ko T, Fujita K, Nomura S, Uemura Y, Onoue K, Hamano M, Katoh M, Yamada S, Katagiri M, Zhang B, Hatsuse S, Yamada T, Inoue S, Kubota M, Sawami K, Heryed T, Ito M, Amiya E, Hatano M, Takeda N, Morita H, Yamanishi Y, Saito Y, Komuro I. Myocardial DNA Damage Predicts Heart Failure Outcome in Various Underlying Diseases. *JACC Heart Fail*. 2023 Oct 28:S2213-1779(23)00680-7.
9. Hosokawa K, Abe K, Funakoshi K, Tamura Y, Nakashima N, Todaka K, Taniguchi Y, Inami T, Adachi S, Tsujino I, Yamashita J, Minatsuki S, Ikeda N, Shimokawahara H, Kawakami T, Ogo T, Hatano M, Ogino H, Fukumoto Y, Tanabe N, Matsubara H, Fukuda K, Tatsumi K, Tsutsui H. Long-term outcome of chronic thromboembolic pulmonary hypertension using direct oral anticoagulants and warfarin: a Japanese prospective cohort study. *J Thromb Haemost*. 2023 Aug;21(8):2151-2162.
10. Purevsuren M, Uehara M, Ishizuka M, Suzuki Y, Shimbo M, Kakuda N, Ishii S, Sumida H, Miyazaki M, Yamashita T, Yoshizaki A, Asano Y, Sato S, Hatano M, Komuro I. Native T1 mapping in early diffuse and limited systemic sclerosis, and its association with diastolic function. *J Cardiol*. 2023 Aug;82(2):100-107.
11. Ishii S, Minatsuki S, Hatano M, Saito A, Yagi H, Shimbo M, Soma K, Fujiwara T, Itoh H, Konoeda C, Sato M, Takeda N, Daimon M, Nakajima J, Komuro I. The ratio of TAPSE to PASP predicts prognosis in lung transplant candidates with pulmonary arterial hypertension. *Sci Rep*. 2023 Mar 7;13(1):3758.
12. Ishii S, Fujiwara T, Yagi H, Takeda N, Ando M,

- Yamauchi H, Inuzuka R, Taniguchi Y, Hatano M, Komuro I. A novel pathogenic variant located just upstream of the C-terminal Ser423-X-Ser425 phosphorylation motif in SMAD3 causing Loeys-Dietz syndrome. *Mol Genet Genomic Med*. 2023 Dec;11(12):e2257.
13. Yagi H, Amiya E, Uehara M, Minatsuki S, Hatano M, Takeda N, Akazawa H, Komuro I. Coronary Periarteritis and Pericardial Thickening Could Be Predictors for Coronary Artery Events Complicated by IgG4-Related Disease. *CJC Open*. 2023 Mar 17;5(6):480-489.
 14. Tsuji M, Kakuda N, Bujo C, Saito A, Ishida J, Amiya E, Hatano M, Shimada A, Imai H, Kimura M, Ando M, Kinoshita O, Yamauchi H, Komuro I, Ono M. Prophylactic negative pressure wound therapy is not effective for preventing driveline infection following left ventricular assist device implantation. *Artif Organs*. 2023 Mar;47(3):566-573.
 15. Inoue S, Ko T, Nomura S, Yamada T, Zhang B, Dai Z, Jimba T, Katoh M, Ishida J, Amiya E, Hatano M, Takeda N, Morita H, Ono M, Komuro I. Compound Heterozygous Truncating Variants in the *BAG5* Gene As a Cause of Early-Onset Dilated Cardiomyopathy. *Circ Genom Precis Med*. 2023 Dec;16(6):e004282.
 16. Kakuda N, Amiya E, Hatano M, Ishida J, Tsuji M, Bujo C, Yagi H, Fujita K, Ishii S, Isotani Y, Kurihara T, Numata G, Gyoten T, Shimada S, Ando M, Ono M, Komuro I. Effect of renal function under left ventricular assist device support on the cardiac function and clinical events after heart transplantation. *Clin Transplant*. 2023 Dec;37(12):e15107.
 17. Hosokawa K, Watanabe H, Taniguchi Y, Ikeda N, Inami T, Yasuda S, Murohara T, Hatano M, Tamura Y, Yamashita J, Tatsumi K, Tsujino I, Kobayakawa Y, Adachi S, Yaoita N, Minatsuki S, Todaka K, Fukuda K, Tsutsui H, Abe K; KABUKI Investigators. A Multicenter, Single-Blind, Randomized, Warfarin-Controlled Trial of Edoxaban in Patients With Chronic Thromboembolic Pulmonary Hypertension: KABUKI Trial. *Circulation*. 2023 Nov 13.
 18. Gyoten T, Amiya E, Kinoshita O, Tsuji M, Kimura M, Hatano M, Ono M. Clinical outcomes of continuous flow left ventricular assist device therapy as bridge to transplant strategy in muscular dystrophy: a single-center study. *Gen Thorac Cardiovasc Surg*. 2023 Jun;71(6):347-353.
 19. Yanase T, Hatano M, Bujo C, Tsuji M, Ishida J, Amiya E, Okamoto K, Ando M, Shimada S, Kinoshita O, Fukushi S, Yamada S, Ono M, Komuro I. Successful Treatment with Letemovir in a Heart Transplant Recipient with UL97 Mutation Ganciclovir-Resistant Cytomegalovirus Colitis and Viremia. *Int Heart J*. 2023 Mar 31;64(1):95-99.
 20. Hirose K, Minatsuki S, Saito A, Yagi H, Takeda N, Hatano M, Komuro I. Impact of psychiatric disorders on the hemodynamic and quality of life outcome of balloon pulmonary angioplasty in patients with chronic thromboembolic pulmonary hypertension: a retrospective study. *Respir Res*. 2023 Nov 11;24(1):274.
 21. Sawano S, Miura M, Higashikuni Y, Saigusa H, Koder S, Takeda N, Hatano M, Ando J, Ono M, Komuro I. Clinical valve thrombosis and arterial embolism in a cancer patient after transcatheter aortic valve replacement. *Oxf Med Case Reports*. 2023 Nov 28; 2023(11):omad125. doi: 10.1093/omcr/omad125.
 22. Shindo A, Ueda K, Minatsuki S, Nakayama Y, Hatsuse S, Fujita K, Nomura S, Hatano M, Takeda N, Akazawa H, Komuro I. Novel *AGL* variants in a patient with glycogen storage disease type IIIb and pulmonary hypertension caused by pulmonary veno-occlusive disease: A case report. *Front Genet*. 2023 Mar 23;14:1148067.
 23. Kurihara T, Amiya E, Hatano M, Ishida J, Minatsuki S, Inoue S, Nomura S, Morita H, Komuro I. Multivessel Coronary Artery Dissection in a Patient with Co-Occurrence of Aortic Dissection and Dilated Cardiomyopathy in the Postpartum Period. *Diseases*. 2023 Dec 10;11(4):178.

Department of Clinical Genomics

Director & Professor

Katsutoshi Oda, M.D., Ph.D.

Project Associate Professor

Hidenori Kage, M.D., Ph.D.

Associate Professor

Aya Ushiku, M.D., Ph.D.

Organization

The Department of Clinical Genomics started as a special unit providing clinical genomics services in 2003. The department functions as the core unit to provide genetic counseling services to support an appropriate and efficient application of genetic testing, as well as genomic medicine in cancer. The department also provides a training program for physicians preparing for board-certified clinical geneticists. Many medical staffs with diverse specialties including pediatricians, obstetricians, neurologists, cardiologists, diabetologists and surgeons participate in the activities of the Department.

Activities

Genetic Counseling

The room (Room 200) is specifically allocated in the outpatient clinic. Genetic counseling is performed by a team of board-certified clinical geneticist and certified genetic counselors in cooperation with other clinical departments. All cases are reviewed and discussed at the conference which is held once every month. We also provide support to clinical departments for establishing genetic diagnosis in various types of diseases, including neurological disorder, pediatric and perinatal disorders, Marfan's Syndrome and Hereditary Breast and Ovarian Cancer.

Genomic Medicine in Cancer

We provide cancer genomic profiling (clinical

sequencing) for incurable malignant solid tumors with 12 collaborative hospitals, as a "Cancer Genome Core Hospital". Two types of cancer genomic profiling (OncoGuide™ NCC Oncopanel System, FoundationOne® CDx Cancer Genomic Profiling) were approved by PMDA in June, 2019. FoundationOne® Liquid CDx Cancer Genomic Profiling was also approved in 2021. As well, we provide an original multiplex genome sequencing, named "Todai OncoPanel", which is composed of DNA panel and RNA panel. The Todai OncoPanel was approved as a name of "GenMineTOP" in 2023. The room (Room 202) is specifically allocated in the outpatient clinic for genomic medicine in cancer (twice weekly).

Publications

1. Matsumoto Y, Kage H, Morota M, Zokumasu K, Ando T, Maemura K, Watanabe K, Kawakami M, Hinata M, Ushiku T, Nakajima J, Nagase T: Integrin alpha 2 is associated with tumor progression and postoperative recurrence in non-small cell lung cancer. *Jpn J Clin Oncol* **53**:63-73, 2023.
2. Sato A, Kobayashi M, Yusa N, Ogawa M, Shimizu E, Kawamata T, Yokoyama K, Ota Y, Ichinohe T, Ohno H, Mori Y, Sakaida E, Kondo T, Imoto S, Nannya Y, Mitani K, Tojo A: Clinical and prognostic features of Langerhans cell histiocytosis in adults. *Cancer Sci* **114**:3687-3697, 2023.

3. Xi Q, Kage H, Ogawa M, Matsunaga A, Nishijima A, Sone K, Kawana K, Oda K: Genomic Landscape of Endometrial, Ovarian, and Cervical Cancers in Japan from the Database in the Center for Cancer Genomics and Advanced Therapeutics. *Cancers (Basel)* **16** (1):136, 2023.
4. Shigeta S, Shimada M, Suzuki S, Kajiyama H, Oda K, Takehara K, Mandai M, Aoki D, Enomoto T, Okamoto A: An Attempt to Develop a New Treatment Strategy for Rare Refractory Gynecological Malignancies: The Japanese Gynecologic Oncology Group. *JMA J* **6**:527-531, 2023.
5. Matsubara J, Mukai K, Kondo T, Yoshioka M, Kage H, Oda K, Kudo R, Ikeda S, Ebi H, Muro K, Hayashi R, Tokudome N, Yamamoto N, Muto M: First-Line Genomic Profiling in Previously Untreated Advanced Solid Tumors for Identification of Targeted Therapy Opportunities. *JAMA Netw Open* **6**:e2323336, 2023.
6. Kage H, Oda K, Muto M, Tsuchihara K, Okita N, Okuma Y, Kikuchi J, Shirota H, Hayashi H, Kokuryo T, Sakai D, Hirasawa A, Kubo M, Kenmotsu H, Akiyama N, Shinozaki-Ushiku A, Tanabe M, Ushiku T, Miyagawa K, Seto Y: Human resources for administrative work to carry out a comprehensive genomic profiling test in Japan. *Cancer Sci* **114**:3041-3049, 2023.
7. Kage H, Shinozaki-Ushiku A, Ishigaki K, Sato Y, Tanabe M, Tanaka S, Tanikawa M, Watanabe K, Kato S, Akagi K, Uchino K, Mitani K, Takahashi S, Miura Y, Ikeda S, Kojima Y, Watanabe K, Mochizuki H, Yamaguchi H, Kawazoe Y, Kashiwabara K, Kohsaka S, Tatsuno K, Ushiku T, Ohe K, Yatomi Y, Seto Y, Aburatani H, Mano H, ORCID: 0000-0003-4645-0181, Miyagawa K, Oda K: Clinical utility of Todai OncoPanel in the setting of approved comprehensive cancer genomic profiling tests in Japan. *Cancer Sci* **114**: 1710-1717, 2023.
8. Saito Y, Kage H, Kobayashi K, Yoshida M, Fukuoka O, Yamamura K, Mukai T, Oda K, Yamasoba T: TERT promoter mutation positive oral cavity carcinomas, a clinically and genetically distinct subgroup of head and neck squamous cell carcinomas. *Head Neck* **45**(12): 3107-3118, 2023.
9. Kobayashi K, Saito Y, Kamogashira T, Kage H, Fukuoka O, Yamamura K, Mukai T, Oda K, Yamasoba T: Survival analysis of high-grade salivary gland carcinoma adjusted for length bias due to delay in comprehensive genomic profiling. *Jpn J Clin Oncol* **53**:1092-1093, 2023.
10. Kobayashi K, ORCID: 0000-0002-5823-3718, Saito Y, Kage H, Fukuoka O, Yamamura K, Mukai T, Oda K, Yamasoba T: CDK12 alterations and ARID1A mutations are predictors of poor prognosis and therapeutic targets in high-grade salivary gland carcinoma: analysis of the National Genomic Profiling Database. *Jpn J Clin Oncol* **53**:798-807, 2023.
11. Komura A, Taguchi A, Ikemura M, Nishijima A, Miyamoto Y, Tanikawa M, Sone K, Mori M, Oda K, Osuga Y: A case of refractory pelvic squamous cell carcinoma of unknown primary that responded to nivolumab. *J Obstet Gynaecol Res* **49**:1300-1304, 2023.

Department of Child Psychiatry

Associate Professor

Yukiko Kano, M.D., Ph.D.

Assistant Professor

Yu Hamamoto, M.D., Ph.D., Kouta Sasaki, M.D.

Homepage <http://kokoro.umin.jp/>

Introduction and Organization

The Department of Child Psychiatry was established in April 2005 as the clinical counterpart to the Clinical Education Center of Mental Development, both of which are funded by the special grant for faculty development. The major aim of the Clinical Education Center is to train mental health specialists in various fields with a fundamental grounding in child psychiatry and neurosciences. Much of the services provided are based on the 39 years of experience in intervention and treatment for developmentally disabled children established in the former child psychiatry division of Department of Neuropsychiatry. Our department uses a multidisciplinary approach by working in collaboration not only with the Department of Neuropsychiatry, Department of Pediatrics and Graduate School of Education in the University of Tokyo but also several other educational and/or clinical facilities on mental development or developmental disorders. The Department of Child Psychiatry complemented the Clinical Education Center by providing fieldwork for clinical training and offered clinical services to patients with various development problems also.

The Clinical Education Center of Mental Development was closed in March 2010 because of time limit of the fund, and Department of Child Neuropsychiatry, Graduate School of Medicine was established in April 2010. The Department of Child Psychiatry, as the clinical counterpart to the department in graduate school, focuses on clinical activity related to research as well as quality practice of child psychiatry and education of leading child psychiatrists and allied

professionals. In addition to professors of the graduate school, 2 psychiatrists and 3 psychologists (2 full-time ones for a definite term and 1 part-time one) are officially assigned to the Department of Child Psychiatry. One psychiatric social worker works mainly for the Department of Child Psychiatry since 2013 also.

Clinical activities

In the year 2023, 8 psychiatrists and 6 psychologists (full-time and part-time) and 1 psychiatric social worker are in charge of treatment at the Department of Child Psychiatry. Although patients with various disorders are seen, the focus of the department is mainly on patients with developmental disorders. We offer services to patients with a broad range of developmental disorders including Autism Spectrum Disorder (ASD), Attention-Deficit/Hyperactivity Disorder (ADHD), Learning Disabilities (LD), Intellectual Disability (ID), tic disorders, and child & adolescent Obsessive-Compulsive Disorders (OCD).

Number of new patients in 2023 was 231, which is slightly higher than 213 in 2022. Out of 231 patients, children of elementary school age were 100, and children of junior high school age were 28. In other words, children of elementary or junior high school age were more than half of the patients. Number of preschool children was 72, suggesting our response to ongoing needs for early diagnosis and intervention.

The follow-up clinic consisted of general clinic and special clinic (Tic/OCD clinic). At the general clinic, a rigorous diagnosis based on detailed assessment and decision about treatment course are provided for

children and adolescents with any kinds of mental problems. After fine adjustment of treatment course within a given period, the patients are referred to community hospitals/clinics or intervention/education facilities with a detailed report. The special clinic meets a need for high level services and works with research for special diseases.

Services for the general child psychiatry outpatients are provided by psychiatrists in the areas of pharmacotherapy, psychotherapy, psychoeducation and also work closely with the schools and community.

Psychologists have charge of psychological consultation as well as psychological examination. Patients involved in those are mainly individuals with developmental disabilities, and individualized treatment focusing on developmental viewpoint is planned for each. Psychological consultation includes services in the following areas: (1) evaluation of cognitive and behavioral development, (2) individualized treatment of the disabled individual (3) counseling of parents and providing information to the disabled individual's support network (relatives, schools) and environmental coordination. In addition to psychologists, psychiatric social worker participates in actual environmental coordination. Cognitive behavior therapy for obsessive-compulsive symptoms or anxiety is sometimes provided also.

As for intervention for preschool children with ASD, intensive individualized therapy consisting of weekly 10 sessions was provided for children aged 3 years or younger.

Parent-training for parents with ADHD children, which started in 2011, was provided. This program aimed that the parents learn deeper understanding of difficult children and appropriate strategy of coping with them.

In addition to these outpatient services, "inpatient assessment on developmental disorders" program started in 2010. This program is provided in the inpatient ward of neuropsychiatry for adolescents or adults who have mental problems such as depression and wish a detailed examination about possibility of hidden developmental disorders including ASD and ADHD. Based on this assessment, psychoeducation on strategies coping with problems related to developmental disorders is provided to patients and their families.

We also focus on psychiatric liaison activity with other departments in the University hospital, especially pediatrics.

Furthermore, as a cross-department and cross-divisional activity, Children, AYA and Family centered Mental Care Center was established in January 2022, and we are playing a central role in its practice.

Education

Undergraduates of the University of Tokyo have opportunities to participate in an assessment and diagnosis session at the general first visit outpatient clinic and intervention for preschool children. Graduate students in clinical psychology course from the University of Tokyo participate in intervention for preschoolers also.

One month training course is offered to junior residents especially in pediatric specialty course. This course includes intake interview of first visit patients, attendance for assessment and treatment for follow-up patients, intervention for preschoolers, and the parent-training. Eighteen residents participated in this course. For general psychiatrists including senior residents of the Department of Neuropsychiatry, an inpatient program of assessment about developmental disorders is provided as opportunity to get knowledge and experience of developmental disorders.

Research

We participate in investigation of etiology and development of effective treatment on ASD and ADHD, which are organized in collaboration with the Department of Neuropsychiatry and other research, educational and clinical facilities. In addition, research related specifically to the clinical activities in the Department of Child Psychiatry is currently being investigated.

Clinical evaluation and treatment

Effectiveness study of early intervention for autistic preschoolers is being undertaken. We focused on investigating early intervention including treatment for children and parent support.

We are also considering support for transition from kindergarten/nursery school to elementary school for children with ASD.

We are also analyzing the data obtained from “inpatient assessment on developmental disorders” program.

In order to develop predictor of parent training for ADHD, we are collecting and analyzing data.

The possible relations among clinical characteristics such as tics and obsessive-compulsive symptoms in Tourette syndrome (chronic tic disorder with multiple motor tics and one or more vocal tics) and child & adolescent OCD are being evaluated. We continue to follow a clinical cohort of patients with Tourette syndrome and are also investigating the impact of COVID-19 on them.

Comprehensive Behavioral Intervention for Tics (CBIT) is provided for children and adolescents with Tourette syndrome, and investigation of its effectiveness is undertaken. We have developed internet-based psychoeducational materials that will lead to CBIT, and are evaluating their effectiveness also.

Multi-institutional collaborative study about treatment-refractory Tourette syndrome in which severe tics persist even after adulthood are conducted with multidisciplinary professionals including neurosurgeons who perform deep brain stimulation.

We are also continuing to analyze the findings of our survey of tics and related behaviors in community preschoolers.

Neuropsychological research

Neuropsychological data on ASD, ADHD and Tourette syndrome are being collected. Analysis of the relations among neuropsychological findings and the clinical evaluation are being conducted.

Neuroimaging

Studies include structural MRI, Near-Infrared Spectroscopy (NIRS) and functional MRI with exploring the pathogenesis of developmental disorders such as ASD and ADHD.

References

1. Ishii-Takahashi A, Kawakubo Y, Hamada J, Nakajima N, Kawahara T, Hirose A, Yamaguchi R, Kuwabara H, Okada T, Kano Y. Changes in child behavioral problems and maternal attachment towards children with attention-deficit/hyperactivity disorder following behavioral parent training: A pilot study. *Psychiatry Clin Neurosci*, 77(7): 412-413, 2023.
2. Yamaguchi R, Kawahara T, Kotani T, Yazawa R, Suzuki A, Kano Y, Ishii-Takahashi A. The effectiveness of exercise programs accessible from home on children's and adolescents' emotional well-being: Systematic review & meta-analysis. *PCN Rep*, 2(2): e103, 2023.
3. Kageyama M, Yokoyama K, Ichihashi K, Noma S, Hashimoto R, Nishitani M, Okamoto R, Solomon P. A peer-led learning program about intimate and romantic relationships for persons with mental disorders (AIRIKI): co-creation pilot feasibility study. *BMC Psychiatry*, 23(1): 767, 2023.
4. Hasegawa N, Yasuda Y, Yasui-Furukori N, Yamada H, Hori H, Ichihashi K, Takaesu Y, Iida H, Muraoka H, Kodaka F, Iga JI, Hashimoto N, Ogasawara K, Ohi K, Fukumoto K, Numata S, Tsuboi T, Usami M, Hishimoto A, Furihata R, Kishimoto T, Nakamura T, Katsumoto E, Ochi S, Nagasawa T, Atake K, Kubota C, Komatsu H, Yamagata H, Ide K, Takeshima M, Kido M, Kikuchi S, Okada T, Matsumoto J, Miura K, Shimazu T, Inada K, Watanabe K, Hashimoto R. Effect of education regarding treatment guidelines for schizophrenia and depression on the treatment behavior of psychiatrists: A multicenter study. *Psychiatry Clin Neurosci*, 77(10): 559-568, 2023.
5. Hashimoto N, Yasui-Furukori N, Hasegawa N, Ishikawa S, Hori H, Iida H, Ichihashi K, Miura K, Matsumoto J, Numata S, Kodaka F, Furihata R, Ohi K, Ogasawara K, Iga JI, Muraoka H, Komatsu H, Takeshima M, Atake K, Kido M, Nakamura T, Kishimoto T, Hishimoto A, Onitsuka T, Okada T, Ochi S, Nagasawa T, Makinodan M, Yamada H, Tsuboi T, Yamada H, Inada K, Watanabe K, Hashimoto R. Change of prescription for patients with schizophrenia or major depressive disorder during admission: real-world prescribing surveys from the effectiveness of guidelines for dissemination and education psychiatric treatment project. *BMC Psychiatry*, 23(1): 473, 2023.

6. Onitsuka T, Okada T, Hasegawa N, Tsuboi T, Iga JI, Yasui-Furukori N, Yamada N, Hori H, Muraoka H, Ohi K, Ogasawara K, Ochi S, Takeshima M, Ichihashi K, Fukumoto K, Iida H, Yamada H, Furihata R, Makinodan M, Takaesu Y, Numata S, Komatsu H, Hishimoto A, Kido M, Atake K, Yamagata H, Kikuchi S, Hashimoto N, Usami M, Katsumoto E, Asami T, Kubota C, Matsumoto J, Miura K, Hirano Y, Watanabe K, Inada K, Hashimoto R. Combination Psychotropic Use for Schizophrenia With Long-Acting Injectable Antipsychotics and Oral Antipsychotics: A Nationwide Real-World Study in Japan. *J Clin Psychopharmacol*, 43(4): 365-368, 2023.

Department of Pain and Palliative Medicine

Associate Professor

Masahiko Sumitani, M.D., Ph.D.

Lecturer

Hiroaki Abe, M.D, Ph.D.

Homepage <https://www.h.u-tokyo.ac.jp/english/centers-services/central-clinical-facilities/department-of-palliative-medicine/index.html>

History and outline of organization

About a half of the cancer patients die by cancer though of the recent innovations of anti-cancer treatments. It mainly depends on the efficacy of the first-line strategies whether cancer is curable or not. Almost all the cancer patients whose initial treatment was unsuccessful die after the distressing struggle against their disease within several years. It is clear for such patients that both sufficient anti-cancer treatments and appropriate approaches to improve their quality of life (QOL) are simultaneously indispensable.

However in our nation, most attention has been entirely paid to the improvement of cure rate and survival time of cancer patients. On the other hand, we have to consider that their QOL is scarcely concentrated until quite recently.

Palliative care means the combination of active therapeutic approach and total human care for the patients no matter which their cancer does or does not respond to anti-cancer treatments. Pain relief, other symptom management, psychological, social and spiritual cares are as a top priority for these patients. It is also emphasized that palliative care is necessary to be applied in the cancer treatment even for patients in early stage of their diseases as well as the progressive or terminal phase of their clinical courses.

In Department of Pain and Palliative Medicine of The University of Tokyo Hospital, we pain and palliative

care team takes a leading role not only to control physical symptoms of cancer patients but also to care for the mental and social support at the same time, and to improve the overall QOL of patients. Moreover, we also promote the education, research and innovation of pain and palliative medicine of our hospital and university.

Palliative care is described clearly in the law "Cancer Control Act" approved by the National Diet on June 2006 that "The medical treatment to aim at relieving many kinds of pain and problems of cancer patients is applicable from the early course of the illness".

Consultation

In The University of Tokyo Hospital, we pain and palliative care team are composed of many kinds of specialists containing three full-time staff doctors, two full-time doctors, and two certificated cancer and hospice care nurses who take an initiative in this multidisciplinary team. We visit to bedsides, consultation rooms and everywhere in the hospital, and offer palliative care to cancer patients who have received cancer care in cooperation with patients' attending doctors, ward staff, therapists of rehabilitation, social workers and every kind of professionals.

The annual number of consultation by our pain and palliative care team is getting increased. In 2019, the numbers achieved to more than total 1000 cases per year and further increased. To date we have become to

collaborate with almost all departments treating cancer in our hospital. These results indicate that the hospital understands the significance of palliative care well and relies on our team.

Education

In the Department of Pain and Palliative Medicine, junior residents of the first and second year can learn the basic knowledge and practice of palliative care by selecting an optional subject for one, two, four or eight months. And then they can participate in the pain and palliative care team and attend the daily team-conference on weekdays.

1) Palliative care training program

The training course (selection) for one or two months

- Program to acquire basic knowledge and practice of palliative care for targeting all junior residents.
 - * Only in "Comprehensive Internal Medicine" selection.

2) Curriculum

Contents of training

- All junior residents are assigned to the pain and palliative care team. They chiefly participate in palliative care practice as a member of the team. They learn to make palliative care plans for inpatients, discuss palliative care of the cases with patients' attending doctors, ward staff, and execute these palliative care plans.

Goal to attain

- Palliative care for inpatients (around 40 cases a day): They acquire the outline of control of physical and psychiatric symptoms of the patients with common diseases in our country such as digestive cancers. They also learn the outline of spiritual and family care.
- Cancer registry: In The University of Tokyo Hospital, it is not unusual that the patient whom the pain and palliative care team treats is often in an end stage, and his or her condition changes physically and mentally day by day. Residents should input the clinical data about palliative care of such patients concisely to the database. They acquire the outline of data management of the palliative care connected directly to a clinical

research.

- Communicative competence: The clinician often has to break "Bad news" to his patients time after time along the course of their illness. It is very difficult for the clinician to provide the appropriate information about diagnoses, recurrence, progression and prognosis of illness to his patients.

The oncologist has to deal with patients' strong grief and feeling of loss when their illness is obviously progressive as well as has to manage both their accepting realities and expecting hopes. We practice according to the guidelines of communication that is recommended by the Japanese Psycho-Oncology Society.

Educational

- In the intensive course for the first-year residents, we prepare lectures about:
 - # pain management
 - # diagnoses and management of delirium
 - # Introduction of guidelines in the field of palliative medicine and their use
 - # Basic medication for palliative care
 - # Spirituality and whole person care for Japanese patients facing death

Daily and weekly schedule

- Conference: Monday-Friday (every weekday); 9:00-10:30am
- Consultation: Monday-Friday (every weekday); from the end of morning conference, up to the completion of all the requested consulting of the day.
- The cancer registry: They input data in the ward round with the HIS (Hospital information system) terminal on each floor.

The instruction system

- Inpatient care: Residents participate in the consultation team (pain and palliative care team) that contains medical instructors. We pain and palliative care team take charge of about 40-50 inpatients usually.
- Multidisciplinary conference: Psychiatrists, pain clinicians/Anesthesiologists, orthopaedicians, pharmacists, medical social workers and others participate in the daily or weekly conference besides the regular member of the pain and palliative care team. Residents can discuss actively the multidisciplinary palliative care plans which our team should carry out. Participants from each

occupation also guide the care plans from their viewpoints of experts.

Research

The clinical information accumulated from the palliative care consultation is input to the concise database simultaneously and utilized for various kinds of clinical researches to submit to the international medical journal such as "International Journal of Radiation Oncology Biology Physics", "Journal of Pain and Symptom Management" and so on.

To date, we the Department of Palliative Medicine have contributed to the progress of following fields of investigations. Please refer to our homepage for results in details and acquisition of the research fund.

- 1) Evaluation and quality assurance of special pain and palliative care team
- 2) Cancer Survivorship
- 3) Investigating cognitive dysfunction induced by pain
- 4) Cancer treatments-induced neurological side effect
- 5) Synergistic influence between sleep disorder and pain
- 6) Assessment of neuropathic pain
- 7) Relationships among our university hospital and local hospitals and clinics
- 8) Palliative care supporting metastatic breast cancer patient
- 9) In palliative medicine field, clinical researches and questionnaires

Publications

1. Abe H, Sumitani M, Matsui H, Inoue R, Fushimi K, Uchida K, Yasunaga H. Association between hospital palliative care team intervention volume and patient outcomes. *Int J Clin Oncol* 2024; 29: 1602-9
2. Hasegawa-Moriyama M, Morioka Y, Hiroi S, Naya N, Suzuki Y, Koretake Y, Hara E, Abe H, Uchida K, Sumitani M. High prevalence of severe pain is associated with low opioid availability in patients with advanced cancer: Combined database study and nationwide questionnaire survey in Japan. *Neuropsychopharmacology Reports* 2024; 44: 502-11
3. Tsuchiya T, Miyawaki S, Saito K, Yoshimoto S, Segawa M, Ebisawa K, Nishikawa M, Sumitani M, Kurokawa M, Yatomi Y, Saito Y. Associations of refractory spontaneous intracranial hypotension and chronic subdural hematoma with factor XIII deficiency: a case report. *Asian J Neurosurgery* 2024 (in press)
4. Saita K, Sumitani M, Koyama Y, Sugita S, Matsubayashi Y, Ogata T, Ohtsu H, Chikuda H. Neuropathic pain development and maintenance and its association with motor recovery after cervical spinal cord injury. *J Spinal Cord Med* 2024 (in press)
5. Kurisu K, Inada S, Maeda I, Nobata H, Ogawa A, Iwase S, Uchida M, Akechi T, Amano K, Nakajima N, Morita T, Sumitani M, Yoshiuchi K. Effectiveness of anti-psychotics for managing agitated delirium in patients with advanced cancer: a secondary analysis of a multicenter prospective observational study in Japan (Phase-R). *Support Care Cancer* 2024; 32: 147
6. Minato T, Kawai K, Edamura T, Abe H, Sumitani M. A case of secondary trigeminal neuralgia caused by lung adenocarcinoma metastasis on trigeminal nerve roots, which was successfully relieved by opioids. *Mol Clin Oncol* 2024; 20: 26
7. Osumi M, Sumitani M, Iwatsuki K, Hoshiyama M, Imai R, Morioka S, Hirata H. Resting-state electroencephalography microstates correlate with pain intensity with complex regional pain syndrome. *Clin EEG Neurosci* 2024; 55: 121-9
8. Sumitani M, Kimura A, Mochizuki T, Akiyama T, Uranbileg B, Takahashi T, Hirai T, Hayakawa K, Chikuda H, Kurano M. Cerebrospinal fluid lysophosphatidylcholine species for distinguishing narrowing of the lumbar spine. *World Neurosurgery* 2024; S1878-8750(23)01881-8
9. Uragami S, Osumi M, Sumitani M, Fuyuki M, Igawa Y, Iki S, Koga M, Tanaka Y, Sato G, Morioka S. Prognosis of post-stroke pain during rehabilitation depends on the pain quality. *Phys Ther* 2024; 104: pzae055
10. Uranbileg B, Sakai E, Kubota M, Isago H, Sumitani M, Yatomi Y, Kurano M. Development of an advanced liquid chromatography-tandem

mass spectrometry measurement system for
simultaneous shipngolipid analysis. ***Scientific
Reports 2024; 14: 5699***

(And, 12 Japanese articles)

University Hospital

Central Clinical Services

Department of Pharmacy

Professor

Tappei Takada, Ph.D.

Lecturer

Yoshihide Yamanashi, Ph.D., Masashi Honma, Ph.D.

Research Associate

Takahiro Amemiya, Ph.D., Yuki Ikebuchi, Ph.D.,
Hiroshi Miyata, Ph.D., Atsushi Tokuda, M.Sc.,
Yusuke Nagae, M.Sc.

Homepage <http://plaza.umin.ac.jp/~todaiyak/>

Introduction and Organization

We have 8 faculty members, 90 pharmacy staffs, and 9 graduate students and 9 undergraduate students from the faculty of pharmaceutical sciences (as of March 1st, 2024).

Clinical activities

Department of Pharmacy consists of the following six sections:

1) Drug information section

This section offers drug information for questions from medical persons, executes and supports the medicine management to inpatients. In addition, the section prepares materials for pharmaceutical affair committee, where each medicine is discussed whether it should be adopted or deleted. Preparation of several periodicals regarding drug information for clinicians is also included.

2) The dispensing section

After inspecting all prescriptions for contra-indications or improper use, medications are dispensed. Drug information is given to outpatients from this section, using a private room if necessary. The computerized order system is linked with automatic packaging machines for oral medicines, automatic dispensing system and barcode label printer for injection drugs.

3) Pharmaceutical section

This section sterilizes formulations of a pharmaceutical such as injection medicines, instillation medicines and decontaminating chemicals. They prepare capsule medicines, ointment medicines, suppositories, central vein nutrition (IVH) for inpatients and in-home care patients. After strict inspection of prescriptions, they also dispense anti-malignant tumor medicine (database is constructed based on the submitted protocols and patients' information) for all of the administration in the hospital. In order to support advanced medical care, they develop and check formulations (characterization of the uniformity, stability and so on) of the medicine that is quite necessary for certain patients, but is not marketed.

4) Drug matters and drug management section

Drug matter section manages the adoption of medical supplies (in-hospital and out-hospital), periodically reconsiders the adopted medicines, and also manages the accountings of all the medicines and other materials used in our department. This section also takes statistics of every information of drug affairs. Drug management section takes care of supplying and safe-keeping of all the in-hospital medicines (2,776 items), out-patient medicines, anesthetics, muscle relaxation drugs, psychotropic drugs, poison

medicines.

5) Narcotic section

Under the supervision of authorized manager for narcotics (the director of the department of pharmacy), narcotics are properly managed, recorded, reported, inspected and directed. Narcotics are properly arranged and managed at the dispensing section and each medical care section.

6) Ward section

They contribute to the team medical care by providing specialized drug information and sharing them with all the staffs involved in the treatment as follows;

- ① Supporting the proper use of medication by pharmacists stationed at ICU sections.
- ② Arrangement and mixing of injections for patients at the staff station of Hematology and Oncology.
- ③ Investigation of carrying medicines and the adverse effect histories, allergy histories *etc.* at the time of hospitalization. Participation for conferences. Procurement and appraisal of patients' basic information about the disease, compilation of the medicine history. Monitoring of medication guidance and the adverse effect for patients, and compilation of guidance record. Offering the doctor with drug information, prescription design support and detailed contents of medication guidance to each patient.
- ④ Investigation and management of ward stock medicine.
- ⑤ Nutrient support of the patients as a member of NST.
- ⑥ Management of proper use of narcotics as a member of palliative care team.
- ⑦ Management of proper use of antibiotics, rounds of a hospital ward, and training of the staffs as members of ICT and AST.

Statistical Data (fiscal year 2023)

Number of items on in-hospital formulary: 2,776

Number of prescriptions (ps.) filled or preparation (pp.) (annual)

out-patients	:	331,831 ps.
(outside	:	303,788 ps.)
(inside	:	28,043 ps.)

out-patient chemotherapy: 20,249 ps.

in-patients : 236,268 ps.

injection drugs : 187,701 ps.

IVH : 3,864 pp.

chemotherapy : 13,043 pp.

TDM consultations (annual) : 23,950 pp.

Numbers of hospital pharmaceutical cares (annual):
24,917 pp.

Education

The department of pharmacy takes various responsibilities of education with regard to clinical pharmacy, pharmacology, and pharmacokinetics for students and graduate students in the faculty of medicine, in the faculty of pharmacy, and in the school of integrated health sciences. We also have our own half a year post-graduate training course optimized for new pharmacists.

For students in the faculty of medicine, we are in charge of "Pathogenetic and Pathology" as an optional course lecture. We are providing a 3-days practice course as a part of compulsory clinical practice for the M3 or M4 students and teach clinical pharmaceutics and practical knowledge of prescription and risk management to them. For the students in the health sciences and nursing, we are in charge of clinical pharmacokinetics lectures as a part of a compulsory subject, "Pharmacology and Toxicology".

For students in the faculty of pharmacy, we are in charge of lectures for the undergraduate students: "Clinical Pharmacy" (compulsory subject). They are educated for the clinical pharmacology and pharmacokinetics. For 5th grade students in the department of pharmacy (6-year course), we are in charge of hospital training for 11 weeks. For the graduate students, we are in charge of "Special Lecture Basic Pharmaceutical Science IV", "Special Lecture Clinical Science", "Advanced Course of Medical Pharmacy" as a cooperator of the Clinical Pharmacokinetics. Recent trends of the medical pharmacy as well as the practical developments and future visions of the department of pharmacy are presented in this lecture. In addition to them, we accept undergraduate and graduate students from the faculty of pharmaceutical sciences and faculty of medicine. They are doing various research activities.

Six year course education system has been launched in the field of pharmaceutical sciences since 2006. In this system, the clinical training by pharmacists at the hospital is one of the most important curriculums. In 2021, we accepted clinical training students from The University of Tokyo, Tokyo University of Pharmacy and Life Sciences, Showa Pharmaceutical University, Hoshi University, and Musashino University, Tokyo University of Science, Keio University and educated them for 2.5 months. In addition, we have had an original one-year post-graduate training course for pharmacists since long time before starting the 6-year course education system. They learned various practical knowledge and techniques necessary for hospital pharmacists. Such education style is still continuing by shortening the period to half a year. In 2023, 10 pharmacists finished this course.

In addition, we are promoting life-long education of pharmacists in the local area by holding regular technical workshops and seminars.

Research

It is evident that the molecular function of particular element cannot always be assigned to only one function at whole body level, because one to one simple correspondence is not common in our body. It is also true that the understanding of the relationship between drug and its ultimate target is not sufficient to predict the pharmacological/toxicological effects. We need to understand not only the detailed molecular machinery of drug target, but also its environment surrounding the target (ex. other associated proteins, signaling molecules, etc.), where and when it works, and finally how it behaves as functional unit in our body. This is a basic idea trying to understand “living body” as “system”. By further promoting this idea to “system pharmacology”, we will be able to identify a molecular target which is related to the pharmacological/toxicological output in clinical situation or even at early drug development stage. Based on such concept, following projects are now ongoing:

- (1) Ohashi Y, Kuriyama S, Nakano T, Sekine M, Toyoda Y, Nakayama A, Takada T, Kawamura Y, Nakamura T, Matsuo H, Yokoo T, Ichida K. Urate transporter ABCG2 function and asymptomatic hyperuricemia: A retrospective cohort study of CKD progression. *Am J Kidney Dis.* 2023;81:134-44 e1.
- (2) Tomabeche R, Miyasato M, Sato T, Takada T, Higuchi K, Kishimoto H, Shirasaka Y, Inoue K. Identification of 5-carboxyfluorescein as a probe substrate of SLC46A3 and its application in a fluorescence-based *in vitro* assay evaluating the interaction with SLC46A3. *Mol Pharm.* 2023;20:491-99.
- (3) Nara K, Yamamoto T, Sato Y, Yagi K, Kawasaki K, Toriumi T, Takada T, Seto Y, Suzuki H. Low pretherapy skeletal muscle mass index is associated with an increased risk of febrile neutropenia in patients with esophageal cancer receiving docetaxel + cisplatin + 5-fluorouracil (DCF) therapy. *Support Care Cancer.* 2023;31:150.
- (4) Toyoda Y, Miyata H, Uchida N, Morimoto K, Shigesawa R, Kassai H, Nakao K, Tomioka NH, Matsuo H, Ichida K, Hosoyamada M, Aiba A, Suzuki H, Takada T. Vitamin C transporter SVCT1 serves a physiological role as a urate importer: Functional analyses and *in vivo* investigations. *Pflugers Arch.* 2023;475:489-504.
- (5) Matsuo M, Ogata Y, Yamanashi Y, Takada T. ABCG5 and ABCG8 are involved in vitamin K transport. *Nutrients.* 2023;15:998.
- (6) Honma M, Suzuki H. Can molecular dynamics facilitate the design of protein-protein-interaction inhibitors? *Nat Rev Rheumatol.* 2023;19:8-9.
- (7) Yamaguchi R, Yamamoto T, Okamoto K, Harada S, Echizenya M, Tsutsumi T, Takada T. Teicoplanin and vancomycin as treatment for glycopeptide-susceptible enterococcus faecium bacteraemia: A propensity score-adjusted non-inferior comparative study. *J Antimicrob Chemother.* 2023;78:1231-40.
- (8) Nara K, Taguchi A, Yamamoto T, Tsuruga T, Tojima Y, Miyamoto Y, Tanikawa M, Sone K, Mori M, Takada T, Suzuki H, Osuga Y. Efficacy of regional cooling + oral dexamethasone for primary prevention of hand-foot syndrome associated with pegylated liposomal doxorubicin. *Support Care Cancer.* 2023;31:283.
- (9) Nara K, Taguchi A, Yamamoto T, Hara K, Tojima Y, Honjoh H, Nishijima A, Eguchi S, Miyamoto Y, Sone K, Mori M, Takada T, Osuga Y. Heterogeneous effects of cytotoxic chemotherapies

- for platinum-resistant ovarian cancer. *Int J Clin Oncol*. 2023;28:1207-17.
- (10) Toyoda Y, Miyata H, Shigesawa R, Matsuo H, Suzuki H, Takada T. SVCT2/SLC23A2 is a sodium-dependent urate transporter: functional properties and practical application. *J Biol Chem*. 2023;299:104976.
 - (11) Nara K, Yamamoto T, Yamashita H, Yagi K, Takada T, Seto Y, Suzuki H. Prior treatment with oxaliplatin-containing regimens and higher total bilirubin levels are risk factors for neutropenia and febrile neutropenia in patients with gastric or esophagogastric junction cancer receiving weekly paclitaxel and ramucirumab therapy: A single center retrospective study. *BMC Cancer*. 2023;23:979.
 - (12) Kuwabara M, Fukuuchi T, Aoki Y, Mizuta E, Ouchi M, Kurajoh M, Maruhashi T, Tanaka A, Morikawa N, Nishimiya K, Akashi N, Tanaka Y, Otani N, Morita M, Miyata H, Takada T, Tsutani H, Ogino K, Ichida K, Hisatome I, Abe K. Exploring the multifaceted nexus of uric acid and health: A review of recent studies on diverse diseases. *Biomolecules*. 2023;13:1519.
 - (13) Kiyomiya K, Tomabechi R, Saito N, Watai K, Takada T, Shirasaka Y, Kishimoto H, Higuchi K, Inoue K. Macrolide and ketolide antibiotics inhibit the cytotoxic effect of trastuzumab emtansine in HER2-positive breast cancer cells: implication of a potential drug-ADC interaction in cancer chemotherapy. *Mol Pharm*. 2023;20:6130-39.
 - (14) Ohno Y, Oriyama T, Honda A, Kurokawa M, Takada T. Induction of CYP3A activity by dexamethasone may not be strong, even at high doses: insights from a case of tacrolimus co-administration. *J Pharm Health Care Sci*. 2023;9:39.
 - (15) Inoue C, Yamamoto T, Miyata H, Suzuki H, Takada T. Elevation of tacrolimus concentration after administration of methotrexate for treatment of graft-versus-host disease in pediatric patients received allogeneic hematopoietic stem cell transplantation. *J Pharm Health Care Sci*. 2023;9:38.
 - (16) Nakayama A, Kurajoh M, Toyoda Y, Takada T, Ichida K, Matsuo H. Dysuricemia. *Biomedicines*. 2023;11:3169.

Department of Clinical Laboratory

Professor

Makoto Kurano, M.D.

Lecturer

Yuichiro Shirota, M.D., Kosuke Watanabe, M.D.

Masaya Sato, M.D., Koki Nakanishi, M.D.

Associate

Masako Nishikawa, M.D., Hideaki Isago, M.D.,

Megumi Hirokawa, M.D.

Chief Technologist

Yoshikazu Ono, M.T.

Homepage <http://lab-tky.umin.jp/>

Introduction and Organization

Department of Clinical Laboratory consists of the following sections, and the 3rd - generation Laboratory Automation System is in full operation, and ordering of laboratory tests, the flow of samples, operation of laboratory analyzers, quality control of analysis, and data reporting are all controlled by the Laboratory Automation computer system. This system has greatly improved the quality, safety, and efficiency of the laboratory and contributed to both patients and doctors by providing rapid and high-quality laboratory testing.

The 1st Section

This section deals mainly with the maintenance of laboratory system, blood and urine sampling, and urinalysis. In 2023, 220,772 outpatient blood sampling were performed in this section. Furthermore, 277,421 urine samples were examined.

The 2nd Section

This section deals with clinical biochemistry and immuno-serology tests. In 2023, 5,756,494 serum enzyme tests (such as AST and ALT), and 577,317 immunological tests were performed.

The 3rd Section

This section deals with laboratory hematology and diabetes-related tests, and gene analysis tests. In 2023, 1,213,407 samples were examined for complete blood cell counts, cell surface marker analysis, prothrombin time, fibrinogen, glucose, and HbA1C tests.

The 4th Section

This section deals with physiological tests, including circulatory, pulmonary, and neuromuscular function ones. In 2023, 45,539 ECG, 21,313 pulmonary function tests, and 9,975 EEG were performed.

The 5th Section

This section deals with ultrasonography. In 2023, 12,392 echocardiography tests, 14,188 abdominal echography tests, and 11,844 other ultrasonography tests were performed.

Teaching activities

Lectures are given to the fourth and sixth grade medical students on clinical laboratory medicine including hematology, chemistry, endocrinology,

immunology, bacteriology, cardiology, and pulmonary function. The reversed CPC program is presented to the sixth grade students. Clinical clerkship is provided for the sixth year medical students, in small groups of 6-7 students for one-week duration. Elective clerkship is provided for two sixth year medical students, who selected to join the training on clinical laboratory medicine, for four-week duration. In this course, students learn clinical and practical knowledge and techniques on various laboratory tests. The second, third, and fourth grade medical students can join research activities in our department (Free Quarter course).

Students from professional schools also study laboratory medicine under the guidance of members in Clinical Laboratory Center. As educational facilities for certified clinical laboratory physicians, we have been training up many physicians.

Research activities

The main goal of our research projects is the development of new and useful laboratory tests, and elucidation of pathophysiology of diseases through laboratory tests. The present main areas included are:

i) (Patho)physiological roles of lysophospholipid mediators and its application into laboratory medicine, ii) introduction of mass spectrometry into clinical laboratory practice, iii) cancer genomic medicine using next generation sequencing, iv) echocardiographic studies of the pathophysiology of valvular heart disease and the hemodynamics, v) neuroscience research using magnetoencephalography and non-invasive brain stimulation, and vi) promotion of medical-engineering cooperation.

References

Original article:

1. Cotella J, Miyoshi T, Mor-Avi V, Addetia K, Schreckenber M, Blankenhagen M, Hitschrich N, Amuthan V, Citro R, Daimon M, Gutierrez-Fajardo P, Kasliwal R, Kirkpatrick JN, Monaghan MJ, Muraru D, Ogunyankin KO, Park SW, Rodrigues ACT, Ronderos R, Sadeghpour A, Scalia G, Takeuchi M, Tsang W, Tucay ES, Zhang M, Prado AD, Asch FA, and Lang RM. Normative Values of the Aortic Valve Area and Doppler Measurements Using Two-Dimensional Trans-thoracic Echocardiography: Results from the Multicenter World Alliance of Societies of Echocardiography Study. *Eur. Heart J. Cardiovasc Imaging.* , in press.
2. Deng Y, Tay HM, Zhou Y, Fei X, Tang X, Nishikawa M, Yatomi Y, Hou HW., Xiao TH., and Goda K. Studying the efficacy of antiplatelet drugs on atherosclerosis by optofluidic imaging on a chip. *Lab. Chip.* 23:410-420, 2023.
3. Drexler Y, Molina J, Elfassy T, Ma R, Christoffersen C, Kurano M, Yatomi Y, Mariani L, Contreras G, Merscher S, and Fornoni A. Identification of Glomerular and Plasma Apolipoprotein M as Novel Biomarkers in Glomerular Disease. *Kidney Int. Rep.* , in press.
4. Hirabayashi T, Kawaguchi M, Harada S, Mouri M, Takamiya R, Miki Y, Sato, H., Taketomi Y, Yokoyama K, Kobayashi T, Tokuoaka SM, Kita Y, Yoda E, Hara S, Mikami K, Nishito Y, Kikuchi N, Nakata R, Kaneko M, Kiyonari H, Kasahara K, Aiba T, Ikeda K, Soga T, Kurano M, Yatomi Y, and Murakami M. Hepatic phosphatidylcholine catabolism driven by PNPLA7 and PNPLA8 supplies endogenous choline to replenish the methionine cycle with methyl groups. *Cell Rep.* 42: 111940, 2023.
5. Hirose K, Nakanishi K, Daimon M, Yoshida Y, Ishiwata J, Nakao T, Morita H, Di Tullio MR, Homma S, and Komuro I. Prevalence, Determinants and Prognostic Value of Left Atrial Dysfunction in Patients with Chronic Coronary Syndrome and Normal Left Ventricular Ejection Fraction. *Am. J. Cardiol* 187: 30-37, 2023.
6. Kage H, Shinozaki-Ushiku A, Ishigaki K, Sato Y, Tanabe M, Tanaka S, Tanikawa M, Watanabe K, Kato S, Akagi K, Uchino K, Mitani K, Takahashi S, Miura Y, Ikeda S, Kojima Y, Watanabe K, Mochizuki H, Yamaguchi H, Kawazoe Y, Kashiwabara K, Kohsaka S, Tatsuno K, Ushiku T, Ohe K, Yatomi Y, Seto Y, Aburatani H, Mano H, Miyagawa K, and Oda K. Clinical utility of Todai OncoPanel in the setting of approved comprehensive cancer genomic profiling tests in Japan. *Cancer Sci.* 114(4):1710-1717, 2023.
7. Kurano M, Tsukamoto K, Kamitsuji S, Kamatani N, Hasegawa K, Hara M, Ishikawa T, Yatomi Y, and

- Teramoto T. Apolipoprotein D modulates lipid mediators and osteopontin in an anti-inflammatory direction. *Inflamm Res.* ,in press.
8. Lee L, Cotella JI, Miyoshi T, Addetia K, Schreckenber M, Hitschrich N, Blankenhagen M, Amuthan V, Citro R, Daimon M, Gutie'rrrez-Fajardo P, Kasliwal R, Kirkpatrick JN, Monaghan MJ, Muraru D, Ogunyankin KO, Park SW, Tude Rodrigues AC, Ronderos R, Sadeghpour A, Scalia GM, Takeuchi M, Tsang W, Tucay ES, Zhang M, Mor-Avi V, Asch FM, and Lang RM. Normal Values of Left Ventricular Mass by 2D and 3D Echocardiography: Results from the World Alliance Societies of Echocardiography Normal Values Study. *J. Am. Soc. Echocardiogr.* , in press.
 9. Matsumoto Y, Kage H, Morota M, Zokumasu K, Ando T, Maemura K, Watanabe K, Kawakami M, Hinata M, Ushiku T, Nakajima J, and Nagase T. Integrin alpha 2 is associated with tumor progression and postoperative recurrence in non-small cell lung cancer. *Jpn. J. Clin. Oncol.* 53(1): 63-73, 2023.
 10. Seki H, Nakanishi K, Daimon M, Hirose K, Mukai Y, Yoshida Y, Nakao T, Morita H, Di Tullio MR, Homma S, and Komuro I. Epicardial fat accumulation and left heart remodeling in patients with chronic coronary syndrome. *Eur. Heart J. Open.* 3: oeac082, 2023.
 11. Singulane CC, Miyoshi T, Mor-Avi V, Cotella JI, Schreckenber M, Blankenhagen M, Hitschrich N, Addetia K, Amuthan V, Citro R, Daimon M, Gutie'rrrez-Fajardo P, Kasliwal R, Kirkpatrick JN, Monaghan MJ, Muraru D, Ogunyankin KO, Park SW, Tude Rodrigues AC, Ronderos R, Sadeghpour A, Scalia GM, Takeuchi M, Tsang W, Tucay ES, Zhang Y, Asch FM, Lang RM. Age-, Sex- and Race-based Normal Values for Left Ventricular Circumferential Strain from the World Alliance of Societies of Echocardiography Study. *J. Am. Soc. Echocardiogr.* , in press.
 12. Sugimoto N, Morita Y, Sakai E, Yatomi Y, and Kurano M. Modulations of urinary lipid mediators in acute bladder cystitis. *Prostaglandins Other Lipid Mediat.* 164: 106690, 2023.
 13. Yoshida M, Morita K, Fukushima H, Jona M, Nishikawa M, Yatomi Y, Kishino Y, Iwasaki A, Ushiku T, Imadome KI, Honda A, Maki H, and Kurokawa M. Development of Epstein-Barr virus-associated lymphoproliferative disorder and hemophagocytic lymphohistiocytosis during long-term lenalidomide maintenance therapy in multiple myeloma. *Int. J. Hematol.* 117:769-773, 2023.
 14. Yoshida Y, Nakanishi K, Daimon M, Hirose K, Ishiwata J, Kaneko H, Nakao T, Mizuno Y, Morita H, Di Tullio MR, Homma S, and Komuro I. Aortic valve sclerosis and subclinical LV dysfunction in the general population with normal LV geometry. *Eur. J. Prev. Cardiol.* , in press.
 15. Zhou Y, Nishikawa M, Kanno H, Yang R, Ibayashi Y, Xiao TH, Peterson W, Herbig M, Nitta N, Miyata S, Kanthi Y, Rohde GK, Moriya K, Yatomi Y, and Goda K. Long-term effects of Pfizer-BioNTech COVID-19 vaccinations on platelets. *Cytometry A.* 103:162-167, 2023.
 16. Kume Y, Hirowatari Y, Kurano M, Yatomi Y, and Matsushita M. Development of blood collection tubes for glucose measurement using adenosine 3-phosphate and sodium fluoride as glycolytic inhibitors. *Annals of clinical biochemistry.* 30:1-8, 2023.
 17. Shiota Y, Fushimi M, Sekino M, and Yumoto M. Investigating the technical feasibility of magnetoencephalography during transcranial direct current stimulation. *Front Hum Neurosci.* 17:1270605, 2023.
 18. Ishii T, Hamada K, Jubishi D, Hashimoto H, Okamoto K, Hisasue N, Sunohara M, Saito M, Shinohara T, Yamashita M, Wakimoto Y, Otani A, Ikeda M, Harada S, Okugawa S, Moriya K, and Yanagimoto S. Waning cellular immune responses and predictive factors in maintaining cellular immunity against SARS CoV 2 six months after BNT162b2 mRNA vaccination. *Scientific Reports.* 13:1-12, 2023.
 19. Sato M. Impact of a Novel Digital Therapeutics System on Nonalcoholic Steatohepatitis: The NASH App Clinical Trial. *Am J Gastroenterol.* 1;118(8):1365-1372, 2023.
 20. Sato M. Development of a transformer model for predicting the prognosis of patients with hepatocellular carcinoma after radiofrequency ablation. *Hepatol Int.* doi: 10.1007/s12072-023-10585-y. Online ahead of print, in press.

21. Minami T, Sato M, Toyoda H, Yasuda S, Yamada T, Nakatsuka T, Enooku K, Nakagawa H, Fujinaga H, Izumiya M, Tanaka Y, Otsuka M, Ohki T, Arai M, Asaoka Y, Tanaka A, Yasuda K, Miura H, Ogata I, Kamoshida T, Inoue K, Nakagomi R, Akamatsu M, Mitsui H, Fujie H, Ogura K, Uchino K, Yoshida H, Hanajiri K, Wada T, Kurai K, Maekawa H, Kondo Y, Obi S, Teratani T, Masaki N, Nagashima K, Ishikawa T, Kato N, Yotsuyanagi H, Moriya K, Kumada T, Fujishiro M, Koike K, and Tateishi R. Machine learning for individualized prediction of hepatocellular carcinoma development after the eradication of hepatitis C virus with antivirals. *J Hepatol*. S0168-8278(23)00424-5, 2023.
22. Zhang C, Herbig M, Zhou Y, Nishikawa M, Shifat-E-Rabbi M, Kanno H, Yang R, Ibayashi Y, Xiao TH, Rohde GK, Sato M, Kodera S, Daimon M, Yatomi Y, and Goda K. Real-time intelligent classification of COVID-19 and thrombosis via massive image-based analysis of platelet aggregates. *Cytometry A*. 103:492-499, 2023.
23. Matsumura H, Shen LT, Isozaki A, Mikami H, Yuan D, Miura T, Kondo Y, Mori T, Kusumoto Y, Nishikawa M, Yasumoto A, Ueda A, Bando H, Hara H, Liu Y, Deng Y, Sonoshita M, Yatomi Y, Goda K, and Matsusaka S. Virtual-freezing fluorescence imaging flow cytometry with 5-aminolevulinic acid stimulation and antibody labeling for detecting all forms of circulating tumor cells. *Lab Chip*. 23:1561-1575, 2023.
24. Oyama T, Yasunaga M, Jona M, Nishikawa M, Yatomi Y, Honda A, Maki H, Morita K, Masamoto Y, and Kurokawa M. Acalabrutinib and steroid for autoimmune thrombocytopenia due to relapsed chronic lymphocytic leukemia with severe bone marrow infiltration. *J Clin Exp Hematop*. 63:187-192, 2023.
25. Yoshida M, Matsuda K, Taoka K, Honda A, Maki H, Masamoto Y, Jona M, Nishikawa M, Yatomi Y, and Kurokawa M. Expansion of large granular lymphocytes after autologous hematopoietic stem cell transplantation. *Int J Hematol*. 117:839-844, 2023.
26. Aihara M, Irie T, Yasukawa K, Minoura I, Miyauchi N, Nishi M, Katayama N, Miyauchi N, Nishi M, Katayama N, Yachiku K, Jinnouchi H, Kadowaki T, Yamauchi T, Yatomi Y, and Sekimizu K. Development of a high-performance liquid chromatographic glycosylated albumin assay using finger-prick blood samples. *Clin Chim Acta*. Mar 1:542:117272, 2023.
27. Yoshida Y, Jin Z, Russo C, Homma S, Nakanishi K, Ito K, Mannina C, Elkind MSV, Rundek T, Yoshita M, DeCarli C, Wright CB, Sacco RL, and Di Tullio MR. Subclinical left ventricular systolic dysfunction and incident stroke in the elderly: long-term findings from Cardiovascular Abnormalities and Brain Lesions. *Eur Heart J Cardiovasc Imaging*. 24:522-531, 2023.
28. Leibowitz D, Yoshida Y, Jin Z, Nakanishi K, Mannina C, Elkind MSV, Rundek T, Homma S, Sacco RL, and Di Tullio MR. Factors associated with the progression of aortic valve calcification in older adults. *Int J Cardiol*. 381:76-80, 2023.
29. Nakanishi K, Daimon M, Fujiu K, Iwama K, Yoshida Y, Hirose K, Mukai Y, Yamamoto Y, Nakao T, Oshima T, Matsubara T, Shimizu Y, Oguri G, Kojima T, Hasumi E, Morita H, and Komuro I. Prevalence of glucose metabolism disorders and its association with left atrial remodelling before and after catheter ablation in patients with atrial fibrillation. *Europace*. 25:euaad119, 2023.
30. Leibowitz D, Yoshida Y, Jin Z, Mannina C, Homma S, Nakanishi K, Elkind MSV, Rundek T, and Di Tullio MR. Long term aortic arch plaque progression in older adults. *Atheroscler Plus*. 52:18-22, 2023.
31. Yoshida Y, Jin Z, Nakanishi K, Matsumoto K, Homma S, Mannina C, Shames S, Elkind MSV, Rundek T, and Di Tullio MR. Subclinical Left Ventricular Dysfunction and Ventricular Arrhythmias in Older Adults With Normal Ejection Fraction. *J Am Heart Assoc*. 12:e030274, 2023.
32. Mukai Y, Nakanishi K, Daimon M, Iwama K, Yoshida Y, Hirose K, Yamamoto Y, Seki H, Nakao T, Oshima T, Matsubara T, Shimizu Y, Oguri G, Kojima T, Hasumi E, Fujiu K, Morita H, and Komuro I. Prevalence, Associated Factors, and Echocardiographic Estimation of Left Atrial Hypertension in Patients With Atrial Fibrillation. *J Am Heart Assoc*. 12:e030325, 2023.
33. Mannina C, Ito K, Jin Z, Yoshida Y, Russo C,

- Nakanishi K, Elkind MSV, Rundek T, Homma S, and Di Tullio MR. Left Atrial Strain and Incident Atrial Fibrillation in Older Adults. *Am J Cardiol.* 206:161-167, 2023.
34. Hirose K, Nakanishi K, Di Tullio MR, Homma S, Sawada N, Yoshida Y, Hirokawa M, Koyama K, Kimura K, Nakao T, Daimon M, Morita H, Kurano M, and Komuro I. Association between non-alcoholic fatty liver disease and subclinical left ventricular dysfunction in the general population. *Eur Heart J Open.* 3:oead108, 2023.
35. Sawada N, Nakanishi K, Nakao T, Miyoshi T, Takeuchi M, Asch FM, Lang RM, and Daimon M. Normal Values of Echocardiographic Right Ventricular Size and Systolic Function Measurements in a Healthy Japanese Population - Subanalysis of the WASE Study. *Circ Rep.* 5:424-429, 2023.
36. Morita Y, Yokoyama R, Tanaka M, Nakatsuka N, Hisasue T, Ono Y, and Kurano M. Evaluation of the Fully Automated Urine Particle Analyzer UF-1500. *J Clin Lab Anal*, 37 (23-24): e24993, 2023

Department of Pathology

Director

Tetsuo Ushiku, M.D., Ph.D. (Professor, Department of Pathology and Diagnostic Pathology)

Deputy Director

Masako Ikemura, M.D., Ph.D. (Lecturer, Office for “Promotion of CPC Education and General Integrative Medicine”)

Aya Shinozaki-Ushiku, M.D., Ph.D. (Associate Professor, Division of Integrative Genomics)

Project Professor

Takeshi Sasaki, M.D., Ph.D. (Next-Generation Pathology Information Networking)

Lecturer

Mariko Tanaka, M.D., Ph.D.

Hiroyuki Abe, M.D., Ph.D. (Department of Pathology and Diagnostic Pathology)

Research Associate

Ryohei Kuroda, M.D., Ph.D., Masaki Suzuki, Munetoshi Hinata, M.D., Ph.D.,

Yoichi Yasunaga, M.D., Ph.D., Amane Yamamoto, M.D., Ph.D.

Akiko Takase, M.D., Ph.D., Mayu Hakozaki, M.D., Ph.D., Atsushi Kondo, M.D., Ph.D.
(Department of Pathology and Diagnostic Pathology)

Homepage <http://pathol.umin.ac.jp/>

Introduction and Organization

Department of Pathology and Diagnostic Pathology and Department of Pathology of the University of Tokyo Hospital have been organized to function as a unit to perform pathology practice (autopsy, surgical pathology, cytology, molecular testing, etc.) at the University of Tokyo Hospital as well as education and research on human pathology.

We set up Telepathology & Remote Diagnosis Promotion Center (TRDP Center) in 2013.

In February 2018, the University of Tokyo Hospital was selected as one of the core hospitals to promote cancer genomic medicine in Japan. From August 2018 to December 2019, the advanced medical care (category B) named ‘Trial of a multiplex genomic testing by “Todai OncoPanel” for Geneprofilng of

malignant solid tumors’ was conducted which enrolled 200 patients. In addition, comprehensive genomic profiling test covered by public health insurance has started (NCC Oncopanel and FoundationOne CDx in November 2019 and GenMine TOP in August 2023). Our department has several molecular pathologists who are in charge of specimen handling and molecular tumor board (expert panel) to contribute to the promotion of genomic medicine.

Clinical activities

(diagnostic pathology and autopsy)

The annual statistics of the pathology practice in 2023 fiscal year consisted of 17,924 surgical cases, 15,903 cytology, 885 intraoperative histologic diagnosis, 350 intraoperative cytology, 29 autopsy cases (autopsy rate, 6.3%). The numbers of surgical and cytology cases

returned to those before COVID-19 pandemic, while the numbers of intraoperative diagnosis and autopsy cases remained smaller than those before the pandemic. Fortunately, there was no need to limit activity in our department.

The following surgical pathology conferences are regularly held; thoracic organs (Drs. Shinozaki-Ushiku, Suzuki and Hinata in charge), liver and pancreato-biliary tract (Drs. Tanaka and Yamamoto), liver metastasis (Dr. Abe), and female genital tracts (Drs. Ikemura and Takase), breast (Dr. Ikemura), hematology (Dr. Shinozaki-Ushiku), bone and soft tissues (Drs. Ushiku and Yasunaga), kidney (Drs. Abe and Hinata), and skin (Dr. Tanaka).

We provide FFPE specimens suitable for comprehensive genomic profiling test. We also join molecular tumor board (expert panel) which is held every week to present histology of the cases and join the discussion. Conventional companion diagnoses using immunohistochemistry and FISH/DISH are also provided to promote precision medicine.

Our mission is to provide the correct diagnosis as soon as possible. We also perform double check by reviewing the reports and slides of all cases to assure the quality of pathologic diagnosis. Whole slide imaging system have been installed, which enabled us to deposit and review all the biopsy specimens as digital information in daily practice.

We hold autopsy case conferences every Monday. Hospital clinico-pathologic conferences (CPC) are also held every month, in which two cases are discussed. The contents are provided as CPC Digest through the hospital internet.

Teaching activities

The lectures and exercise course of systemic pathology are for the 2nd grade medical students. Clinical Clerkship (CC) courses of autopsy and surgical pathology are for the 3rd and 4th grade medical students. We accepted several medical students in Elective Clerkship course as well as Free Quarter program.

We instructed all clinical residents (junior course) to submit a report of CPC case as an obligatory requirement of their medical training. We have made out the digest version of CPC slides open in the

hospital and started e-learning program for interns to solve the problems in CPC by themselves, thereby facilitating their understanding.

The Department of Pathology accepted four junior residents (total 8 months) in 2023 for their first and second-year program.

Research activities

We are working on the pathologic research projects of neoplastic diseases based on observation obtained from pathologic diagnosis as well as discussion with clinicians at surgical pathology conferences.

To develop AI-based pathology diagnosis system, some projects are currently in progress. Dr. Abe focuses on gastrointestinal tract biopsy diagnosis using machine learning. Dr. Hinata has developed an automatic system to detect immunotherapy-sensitive subtype in gastric cancer using histologic image-based deep learning.

The development of automatic grossing and sectioning system using AI-equipped robot is also in progress as collaborative research with engineering faculty-of the University of Tokyo (Prof. Mamoru Mitsuishi).

We continue the study to investigate the usefulness of post-mortem CT images for hospital autopsy in collaboration with the department of radiology. We obtain post-mortem images with a CT apparatus in the autopsy-assisting CT room and compare the results with those of autopsy to better understand the patients' pathophysiology.

In addition, a lot of collaborative research projects are also being conducted with various departments and laboratories.

References

1. Abe K, Emoto S, Sasaki K, Nozawa H, Yasunaga Y, Ishihara S. Multiple ulcers and perforation of small intestine with everolimus use in a patient with rectal neuroendocrine tumor: A case report. *Int J Surg Case Rep.* 2023;106:108094.
2. Fukushima H, Morita K, Ikemura M, Tanaka M, Nakai Y, Maki H, Suzuki T, Mizuno S, Nakai Y, Kurokawa M. Acute pancreatitis as the initial manifestation of acute myeloid leukemia with

- chromosome 16 rearrangements. *Int J Hematol.* 2023;118(3):381-387.
3. Kanemaru N, Nakai Y, Watadani T, Nakao T, Hinata M, Nakazawa A, Akamatsu N, Ushiku T, Hasegawa K, Abe O. Multimodal imaging findings of intrahepatic cholangiocarcinoma arising from a biliary adenofibroma: a case report with radiological-pathological correlation. *Abdom Radiol (NY).* 2023;48(8):2469-2476.
 4. Kasuga S, Abe S, Nozawa H, Sasaki K, Murono K, Emoto S, Matsuzaki H, Yokoyama Y, Nagai Y, Yoshioka Y, Shinagawa T, Sonoda H, Ushiku T, Ishihara S. Diverticular perforation of terminal ileum associated with chemotherapy for non-small cell lung carcinoma: a case report. *J Surg Case Rep.* 2023;2023(4):rjad179.
 5. Kato H, Kimura S, Taguchi M, Sunouchi T, Hoshino Y, Hidaka N, Foligno NE, Koga M, Manaka K, Tamiya H, Kawakami M, Kage H, Yasunaga Y, Nangaku M, Makita N, Ito N. FGF23-related hypophosphatemia in a patient with small cell lung cancer: a case report and literature review. *Endocr J.* 2023;70(10):1005-1013.
 6. Kobayashi H, Zhang L, Okajima K, Ishibashi Y, Hirai T, Tsuda Y, Ikegami M, Kage H, Shinozaki-Ushiku A, Oda K, Tanaka S. BRAF mutations and concurrent alterations in patients with soft tissue sarcoma. *Genes Chromosomes Cancer.* 2023;62(11):648-654.
 7. Komura A, Taguchi A, Ikemura M, Nishijima A, Miyamoto Y, Tanikawa M, Sone K, Mori M, Oda K, Osuga Y. A case of refractory pelvic squamous cell carcinoma of unknown primary that responded to nivolumab. *J Obstet Gynaecol Res.* 2023;49(4):1300-1304.
 8. Matsumoto H, Shinya Y, Miyawaki S, Shin M, Koizumi S, Sato D, Hinata M, Ikemura M, Kiyofuji S, Kin T, Iwanaga M, Shimizu M, Nakatomi H, Saito N. White epidermoid cyst transformation after stereotactic radiosurgery: illustrative case. *J Neurosurg Case Lessons.* 2023;5(24):CASE2376.
 9. Matsumoto N, Kashio A, Yoshida M, Kondo K, Miyamoto S, Okazaki M, Ikemura M, Ushiku T, Yamasoba T. Cholesterol granuloma in facial nerve canal presenting with facial nerve paralysis. *Auris Nasus Larynx.* 2023; 50(5):799-804.
 10. Obo T, Morita K, Sumida Y, Nakazaki-Watadani K, Ikemura M, Yasaka K, Abe O, Takami H, Takayanagi S, Tanaka S, Maki H, Masamoto Y, Miwa A, Kurokawa M. Isolated relapse of plasma cell leukemia in the central nervous systems: a case report and literature review. *Inter J Hematol.* 2023;118(1):135-140.
 11. Ohara K, Miyawaki S, Nakatomi H, Okano A, Teranishi Y, Shinya Y, Ishigami D, Hongo H, Takayanagi S, Tanaka S, Shinozaki-Ushiku A, Kohsaka S, Kage H, Oda K, Miyagawa K, Aburatani H, Mano H, Tatsuno K, Saito N. Case report and literature review: exploration of molecular therapeutic targets in recurrent malignant meningioma through comprehensive genetic analysis with Todai OncoPanel. *Front Neurol.* 2023;14:1270046.
 12. Ohki D, Tsuji Y, Kuroda R, Ushiku T, Fujishiro M. Gastrointestinal: A case of significant esophageal ulceration due to oral iron pill therapy. *J Gastroenterol Hepatol.* 2023;38(8):1241.
 13. Rai Y, Umekawa M, Shinya Y, Hasegawa H, Katano A, Kondo K, Shinozaki-Ushiku A, Saito N. Stereotactic radiosurgery for recurrent skull base polymorphous adenocarcinoma invading the cavernous sinus: illustrative case. *J Neurosurg Case Lessons.* 2023;5(19):CASE23103.
 14. Sato D, Takami H, Takayanagi S, Taoka K, Tanaka M, Matsuura R, Tanaka S, Saito N. Lymphoproliferative disorder during temozolomide therapy; a representative case of a formidable complication and management challenges. *BMC Neurol.* 2023;23(1):224.
 15. Sato D, Takami H, Takayanagi S, Ikemura M, Matsuura R, Tanaka S, Saito N. Intraventricular central neurocytoma molecularly defined as extraventricular neurocytoma: a case representing the discrepancy between clinicopathological and molecular classifications. *Brain Tumor Pathol.* 2023;40(4):230-234.
 16. Takami H, Mukasa A, Takayanagi S, Koike T, Matsuura R, Ikemura M, Ushiku T, Yoshikawa G, Shibahara J, Tanaka S, Saito N. Correction: Morphologically, genetically and spatially mixed astrocytoma and oligodendroglioma; chrono-

logical acquisition of 1p/19q codeletion and CDKN2A deletion: a case report. *Brain Tumor Pathol.* 2023;40(2):142.

17. Yoshida M, Morita K, Fukushima H, Jona M, Nishikawa M, Yatomi Y, Kishino Y, Iwasaki A, Ushiku T, Imadome KI, Honda A, Maki H, Kurokawa M. Development of Epstein-Barr virus-associated lymphoproliferative disorder and hemophagocytic lymphohistiocytosis during long-term lenalidomide maintenance therapy in multiple myeloma. *Int J Hematol.* 2023;117(5):769-773.

Radiology Center

Professor (Director)

Osamu Abe, M.D., Ph.D.

Associate Professor(Vice Director)

Shiori Amemiya, M.D., Ph.D.

Assistant Professor

Go Shirota, M.D., Ph.D.

Chief Technologist (Vice Director)

Toshihiro Hayashi, R.T.

Homepage <https://www.h.u-tokyo.ac.jp/patient/depts/houshasenbu/>

Introduction and Organization

Radiology Center was established in August 1964 as a part of the Central Clinical Services. Currently, the Department consists of three divisions: Diagnostic Radiology (imaging and intervention), Nuclear Medicine, and Radiotherapy, in addition to Radiation Safety Control Center. The center engages in radiology services such as various imaging examinations, radiotherapy, and radiation safety management.

The members are as follows: Professor Osamu Abe (Director, since Oct. 2016), Shiori Amemiya(Vice Director/Associate Professor), Go Shirota (Assistant Professor), 77 radiology technologists, including Chief Technologist Toshihiro Hayashi, and one technical specialist in charge of radiation control. In addition to the above, Radiology Center is operated in corporation with the staff radiologists, graduate students, and residents of the Department of Radiology, as well as physicians from other departments, nurses, and clinical engineering technicians of the Department of Clinical Laboratory. In recent years, the number of radiological services has increased, and we are trying to cope with this trend by improving work efficiency, optimizing staffing, and introducing new equipment.

The development of technologies for advancing and improving radiological practice is a cooperative effort

between physicians and radiologists. In addition to the fields of imaging and radiation therapy, the construction of image management systems, image processing, and image transfer systems have become essential themes in recent years. The radiology information system (RIS) and diagnostic reporting systems were digitalized in 1994. And a picture archiving and communication system (PACS, the film-less imaging system) was introduced in the hospital in May 2003. To reduce and equalize the burden of radiologists, we started preparing for the trial introduction of a new high-performance diagnostic interpreting system in 2012 and launched a new PACS system with deep learning-based software in 2023. In the field of radiation safety control, stimulated by the need to evaluate the individual accumulated exposure dose by medical radiation, we have started a working group to solve this problem. We provide the individualized accumulated exposure dose data on RIS. We also work for research on new radiology techniques such as image-guided radiation therapy, CT, MRI, PET, flat panel detector, postmortem imaging, artificial intelligence, etc.

Clinical activities

1) Diagnostic Radiology Section:

The diagnostic radiology section is responsible for

simple radiography (bone, chest, abdomen, head, pediatric, breast, pelvic measurement), various radiography with contrast mediums (gastrointestinal tract, urinary tract), radiography in the operating rooms, radiography in the emergency rooms, outpatient radiography, portable radiography in hospital wards, dental and oral radiography, bone mineral content determination, CT, MRI, angiography and interventional radiology (IVR), image processing and analysis (3D image reconstruction and analysis).

Most examinations are performed in the diagnostic radiology section on the 1st floor of the Central Clinical Services Building 1. Some are performed in the MRI rooms, Surgical Center, Critical Care and Emergency Medical Center/ER, and some other departments in the Central Clinical Services Building 2. The number of examinations, especially CT and MRI, is dramatically increasing. Six multi-slice CT machines (2 x 320-row, 1 x 256-row, 1 x 64-row CT, 2 x 80-row), 7 MRI machines (5 x 3T MRI, 2 x 1.5T MRI), 6 angiography systems (including one hybrid angiography system in the Surgical Center) are in use. From April 2023, Interventional Radiology Computed Tomography (IR-CT) is in operation, enabling to provide more advanced IR procedures.

2) Nuclear Medicine Section:

The nuclear medicine section is responsible for various nuclear medicine examinations (gamma camera, single-photon emission computed tomography (SPECT), positron emission tomography (PET)), radiopharmaceutical management, production of PET nuclides using accelerators, label synthesis, quality verification, radioactive contaminant management, and radionuclide therapy.

The nuclear medicine section in Central Clinical Services Building 1 performs various medical services using unsealed radionuclides. Nuclear medicine examinations include conventional scintigraphy (bone, tumor, kidney, thyroid), myocardial SPECT, and brain SPECT. Functional and statistical images using tracer methods are also available. In recent years, the demand for PET examinations has been increasing, especially for ^{18}F -fluorodeoxyglucose-PET (FDG-PET) in cases with malignant tumors. PET examinations using tracers labeled with positron nuclides produced by a small cyclotron are used to evaluate

blood flow and metabolism, receptor imaging, and the presence of amyloid accumulation in the brain. With the opening of the Central Clinical Service Building 2, a PET-CT scanner and a cyclotron were installed. In 2023, we started Amyloid PET to determine the indication for Alzheimer's disease medication and radionuclide therapy for neuroendocrine neoplasm.

3) Radiation Oncology Section:

The radiation oncology section is responsible for high-energy radiotherapy, gamma-knife therapy, brachytherapy, and radioisotope (RI) internal therapy. The radiation oncology section is on the third basement floor of Central Clinical Services Building 2 and has dedicated rooms for RI internal therapy on the 9th floor of the Inpatient Building A.

The radiation oncology section has three linear accelerators (LINAC), an iridium brachytherapy machine, a gamma-knife for stereotactic irradiation of the head, and a CT scanner for treatment planning. A treatment planning system is used to perform radiation therapy. All linear accelerators are equipped with a CT imaging function for position matching, enabling highly accurate image-guided radiation therapy. In 2023, two linear accelerators were upgraded, enabling the delivery of advanced radiation therapies such as Volumetric Modulated Arc Therapy (VMAT), Stereotactic Body Radiation Therapy (SBRT), and Stereotactic Radiosurgery/Radiotherapy. One of these upgraded LINACs is equipped with an optical surface monitoring system, allowing for real-time patient monitoring during treatment and enabling Surface-Guided Radiation Therapy (SGRT), including markerless treatment delivery. Fractionated Gamma Knife treatment has been recently introduced. In addition, a new Radiology Information System (RIS) was implemented in fiscal year 2023 to enhance medical safety and is being used to establish a comprehensive cancer treatment management platform.

4) Others:

The radiation control office handles the hospital's management of X-ray generators, radioactive contaminants, radiation education, and health management (glass badge management, etc.). In addition, it conducts management and operation under

the Act on the Regulation of Radioisotopes and the Medical Care Act.

Conclusion

In 2002, the diagnostic imaging equipment was fully digitalized, and in the following year, a filmless system was realized by distributing images and diagnostic reports via the hospital information system. The Critical Care and Emergency Medical Center/ER, MRI rooms, and the radiation oncology section were relocated to the Central Clinical Service Building 2 (completed in 2006), and the latest equipment was introduced. In January 2018, when Inpatient Building B started operation, a portable radiography system was established.

As a result of the development of digital technology, diagnostic equipment, image processing technology, diagnostic imaging, and radiotherapy technology have become more sophisticated. Radiology Center will continue to contribute to improving the level of medical care at the University of Tokyo Hospital through improved services to other departments.

Publications

See the corresponding part of the Department of Radiology.

Number of examinations in 2022.4 to 2023.3

	Inpatient	Outpatient	Total
Radiography (plain)	94,833	82,259	178,092
Radiography (enhanced)	5,489	1,320	6,809
Angiography	3,541	16	52,431
Computed tomography	14,535	37,896	52,431
Magnetic resonance imaging	4,030	16,283	20,313
Nuclear medicine	1,184	3,534	4,718
Radiotherapy	4070	6806	10876
Bone mineral densitometry	199	2,800	2,999

Rehabilitation Center

Professor

Toru Ogata, M.D.

Lecturer

Sayaka Fujiwara, M.D.

Research Associate

Haruhi Inokuchi, M.D., Kentaro Morita, M.D.,

Ryoko Sawada, M.D.

※The following information is the same as that of the previous year for certain reasons.

Homepage <http://todaireh.umin.ne.jp>

Introduction and Organization

The physical therapy service started in 1963 at the University of Tokyo Hospital, and then expanded to include occupational therapy and social work section. In 1966 this service was converted to the central rehabilitation service department as a part of the Central Diagnostic and Therapeutic Service Department. The Central Rehabilitation Service became an independent unit in 1970. After the reorganization of the University of Tokyo Hospital according to major organic classification in 1998, outpatient clinic as rehabilitation medicine was installed. The formal title of our unit was changed from the Physical Therapy Department to the Rehabilitation Department by the budget measures in the fiscal year 2001, and we integrated the related personnel categories, which belonged to the orthopedic surgery department and the physical medicine department.

At present our department consists of four sections. Rehabilitation physicians' section includes five full-time doctors and two other part-time doctors. They work chiefly for clinical practice in medical rehabilitation service, but also have to engage in teaching activities for medical students. Nineteen physical therapists are working in the physical therapy section. In the occupational therapy section, six

occupational therapists work for the general rehabilitation service and the other four therapists work for the psychiatric rehabilitation. Four acupuncture therapists perform acupuncture and moxibustion. In the Day-care Unit, clinical psychologists and nurses also work. In 2006, speech therapists who had belonged to other departments in the University of Tokyo Hospital were included in our department. From 2009, a speech therapist added to our department, and now three therapists perform therapy for patients with aphasia, dysarthria, and dysphagia.

Clinical activities

The professor serves as a director of Rehabilitation Center, the University of Tokyo Hospital. The Rehabilitation Center and the Department of Rehabilitation Medicine are united and engage in clinical practice. We have at present no charged ward, and treat about 4,700 new referrals annually from almost all the departments of the university hospital. We always take charge of 250-300 patients corresponding about 25-30% of the whole number of inpatients. We also see 15 people per day at the outpatient rehabilitation setting. The numerical ratio of outpatient is being reduced in order to give priority to the clinical service corresponding to needs expansion of service to inpatients.

Teaching activities

We have provided several clinical curriculums on rehabilitation medicine for 4th, 5th, and 6th year medical students since 1973. The systematic lecture series for 4th year medical students (M2) include the subjects on rehabilitation for disorders such as cerebrovascular disturbances, respiratory disorders, neuromuscular diseases, bone and joint diseases, and pediatric disorders as well as on outline of rehabilitation, and amputation/prostheses. We have provided a clinical practice in small group, so-called clinical clerkship for 5th and 6th year students from Wednesday to Friday every week. They experience a few patients and learn how to take a patients' history, physical findings, functional evaluation, and how to plan rehabilitation programs. We have introduced a few of elective students for elective clinical clerkship to our collaborating hospitals with specialized rehabilitation ward.

In addition, we have provided the training of students including physical therapy, occupational therapy, and speech therapy. Twenty students or more come and stay at the university hospital annually as a long-term clerkship from several PT/OT/ST training schools.

Research activities

Our research activities are growing up. In 2006, the Rehabilitation Center moved to the new building and a research laboratory was provided for the first time. As the motion analysis system was partially renewed, we are planning our researches mainly in the field of musculoskeletal disabilities. In addition, we are planning collaborating researches with other departments in our hospital, other faculties in our university, and institutions outside the University of Tokyo. The ongoing and scheduled projects are as follows.

- 1) 3D Motion analysis of patients with musculoskeletal disorders
- 2) Study on the relationship between sensory deficit and motor control
- 3) Rehabilitation and long-term outcome in patients with skeletal dysplasias
- 4) Pathology and treatment for patients with congenital limb deficiencies
- 5) Analysis of rehabilitation outcome using DPC data

References

1. Kojima T, Ishikawa H, Tanaka S, Haga N, Nishida K, Yukioka M, Hashimoto J, Miyahara H, Niki Y, Kimura T, Oda H, Asai S, Funahashi K, Kojima M, Ishiguro N: Validation and establishing targets for the physician-based clinical scale for foot and ankle surgery in patients with long-standing rheumatoid arthritis based on patient-reported outcomes: Results from a multicenter prospective observational cohort study to evaluate the efficacy of joint surgery in the treat-to-target era. *Mod Rheumatol*, Online ahead of print
2. Mano H, Fujiwara S, Haga N: Body knowledge in children with congenital upper limb deficiency. *Brain Nerve* 72(4): 445-451, 2020
3. Mano H, Fujiwara S, Haga N: Effect of prostheses on children with congenital lower limb deficiencies. *Pediatr Int* 62: 1039-1043, 2020
4. Mano H, Fujiwara S, Takamura K, Kitoh H, Takayama S, Ogata T, Haga N: Treatment approaches for congenital transverse limb deficiency: Data analysis from an epidemiological nation survey in Japan. *J Orthop Sci*, Online ahead of print
5. Matsuoka M, Tsukamoto S, Orihara Y, Kawamura R, Kuratani M, Haga N, Ikebuchi K, Katagiri T: Design of primers for direct sequencing of nine coding exons in the human ACVR1 gene. *Bone* 138: 115469, 2020
6. Matsushita M, Mishima K, Yamashita S, Haga N, Fujiwara S, Ozono K, Kubota T, Kitaoka T, Ishiguro N, Kitoh H: Impact of fracture characteristics and disease-specific complications on health-related quality of life in osteogenesis imperfecta. *J Bone Miner Metabol* 38(1): 109-116, 2020
7. Pignolo RJ, Cheung K, Kile S, Fitzpatrick MA, De Cunto C, Al Mukaddam M, Hsiao EC, Baujat G, Delai P, Eekhoff EMW, Di Rocco M, Grunwald Z, Haga N, Keen R, Levi B, Morhart R, Scott C, Sherman A, Zhang K, Kaplan FS: Self-reported baseline phenotypes from the International Fibrodysplasia Ossificans Progressiva (FOP) Association Global Registry. *Bone* 134: 115274, 2020

8. Sawada R, Yamana H, Shinoda Y*, Tsuda Y, Matsui H, Fushimi K, Kobayashi H, Matsubayashi Y, Yasunaga H, Tanaka S, Haga N: Predictive factors of 30-day mortality after surgery for spinal metastasis: Analysis of a nationwide database. *J Orthop Sci* S0949-2658(20)30208-6, 2020, Online ahead of print
9. Shinoda Y, Sawada R, Ishibashi Y, Akiyama T, Zhang L, Hirai T, Oka H, Ohki T, Ikegami M, Okajima K, Okuma T, Kobayashi H, Goto T, Haga N, Tanaka S: Prediction of pathological fracture in patients with lower limb bone metastasis using computed tomography imaging. *Clin Exp Metastasis* 37(5): 607-616, 2020
10. Takeda J, Nanatsue K, Yamagishi R, Ito M, Haga N, Hirata H, Ogi T, Ohno K: InMeRF: Prediction of pathogenicity of missense variants by individual modeling for each amino acid substitution. *NAR Genom Bioinform* 2(2):lqaa038,2020
11. Taya M, Hatano M, Saito A, Nitta D, Maki H, Hosoya Y, Minatsuki S, Tsuji M, Sato T, Murakami H, Narita K, Konishi Y, Watanabe S, Yokota K, Haga N, Komuro I: Clinical importance of respiratory muscle fatigue in patients with cardiovascular disease. *Medicine(Baltimore)* 99(34): e21794, 2020
12. Umezaki S, Shinoda Y, Mukasa A, Tanaka S, Takayanagi S, Oka H, Tagawa H, Haga N, Yoshino M: Factors associated with health-related quality of life in patients with malignant glioma: Impact of symptoms and implications for rehabilitation. *Jap J Clin Oncol* 50(9): 990-998, 2020
13. Haga N, Nakashima Y, Kitoh H, Kamizono J, Katagiri T, Saijo H, Tsukamoto S, Shinoda Y, Sawada R, Nakahara Y: Fibrodysplasia ossificans progressiva: review and research activities in Japan. *Pediatr Int* 62: 3-13, 2020

Surgical Center

Professor (Director)

Kazuhiko Fukatsu M.D., Ph.D.

Lecturer

Yuhei Saito, Ph.D.

Yuki Taniguchi, M.D., Ph.D

Reo Inoue, M.D., Ph.D

Satoshi Murakoshi, M.D., Ph.D.

Assistant Professor

Kenichi Kono, M.D., Ph.D.

Homepage: <https://www.h.u-tokyo.ac.jp/patient/depts/shujutsu/>

Introduction and Organization

Uniform management of operating rooms (OR) first began at the University of Tokyo Hospital in July 1955. The office, so called the surgical center, was located at the Old Central Building until December 1987. The center moved to the new Central Clinical Service Building 1 in January 1988, where there are 12 ORs including one bio-clean room. The surgical center became to provide managerial services of the OR to 18 surgical departments after moving into the new office building. The total number of operations remained to be below 6,300 a year between 1999 and 2000 because of the limitation of number of ORs and nurses.

In July 2001, the branch hospital in Mejiro area was merged with the University of Tokyo Hospital in Hongo area, which opened a new Ward A Building in October 2001. After the merger, the number of elective operations markedly increased and became over 7,300. Two additional ORs began to be used tentatively to accommodate an enormous increase in the number of elective operations. The one OR was set up on the ICU/CCU/HCU floor in the new Ward A Building and the other was in the Outpatient Clinic Building. The outpatient OR for orthopedic outpatients was diverted for the general OR, which was used for the short-stay and day surgery.

Until September 2001, the elective operations had been performed in 9.5 ORs/day on average. After October 2001, 12 ORs/day began to be used. In 2006, the Central Clinical Service Building 2, which had 11 ORs, was completed to solve the shortage of the number of ORs. As a result, the total number of ORs became 23, and then the number of operations has tremendously increased. More recently, “On call PM block time” has been introduced to improve OR utilization. In April 2014, one of the ORs in the Central Clinical Service Building 2 was renovated into a hybrid OR which is equipped with advanced interventional imaging system for the patients undergoing interventional surgical treatment. In August 2020, Day Surgery room was built at ICU-2 area for ophthalmic operation.

A total of 8,485, 9,550, 9,921, 9,944, 10,394, 10,170, 10,752, 11,235, 11,150, 10,960, 11,161, 11,014, 11,124, 11,323, 9,945 (under the circumstance of Covid-19 pandemic), 11,047, 11,456, and 11,869 operations were performed in 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021, 2022 and 2023 fiscal year, respectively. The number of operations in 2021 fiscal year counts for approximately 1.8 times comparing to that in 2001.

These days more and more patients undergo

endoscopic surgery such as laparoscopy/thoracoscopy assisted operation. There is also an apparent increase in the number of patients who are at high risk with critical morbidity or carrier of the particular types of pathogens such as tuberculosis, MRSA, *Pseudomonas aeruginosa*, HBV, HCV and HIV.

Clinical Activities

All operations of in-patients are performed in 23 ORs and Day Surgery room at the surgical center. Computer system has been utilized to handle the information on operation. In May 1999, the on-line system was introduced to order the elective and urgent/emergent operations through the computer terminal in the wards. The input of postoperative patient information started from March 2000. This system also enabled the medical staff to know the availability of the ORs of the next day. From November in 2000, the medical staff can see the operation schedule through the hospital computer network.

The present status of the operation process began to be seen through the computer monitor from May 1997. The photographs of surgical sites, resected organs and live video image began to be delivered to the clinical departments from February 1997.

Hospital logistics system were totally replaced to improve material flow of hospital in October 2001, when supply processing and distribution (SPD) department was established and started its practice. In the surgical center, this SPD system has been available since September in 2002.

Recently, the number of complicated and long surgical procedures using advanced technology has dramatically increased. In addition, more and more patients tend to undergo surgery using artificial implant, joint prosthesis or intraocular lenses. Those operations include organ transplantation, microvascular surgery, cardiovascular surgery, minimally invasive surgery and navigation-guided orthopedic/neurosurgical surgery and stent grafting for the abdominal or thoracic aortic aneurysms. Organ transplantation and intraoperative three-dimensional echo-guided surgery are also frequently performed. Minimally invasive surgery is another recent trend of the operation. Those include endovascular treatment for heart anomalies such as ASD and VSD. More recently, the robotic surgery has

started at the surgical center.

Healthcare-Associated infections (HAIs) are critical issues in the surgical center. It is essential to educate staffs how to prevent HAIs and occupational infections. As the number of operations associated with emerging or re-emerging infectious diseases such as HIV and tuberculosis has increased, all healthcare staff are required to adhere to the principles of standard and/or transmission-based precautions also in the surgical center.

Teaching Activities

The following lectures or seminar are given to the undergraduate and postgraduate medical students: aseptic techniques, sterilization/disinfection methods, prevention of perioperative infections, humoral and cellular responses to trauma and shock, training of scrubbing and gown techniques. The curriculum is updated each year. Introductory course for disinfection, sterilization and preservation of surgical instruments and medical devices was added in the training courses in 1998, which gained more interest and popularity among many students.

In the surgical center, the innovative surgical instruments and medical devices are introduced to perform highly advanced operations such as in the navigation surgery, transplantation surgery, cardiovascular surgery and robotic surgery. As a result, the education related to the assist for those surgical procedure has become most important activities in the surgical center. The lectures of advanced technologies are in the curriculum for the surgeons, the nursing staff and clinical engineers so that they can understand how to use them in a proper way.

Lectures for the nursing staff consist of a freshman course and an advanced course. The freshman course is a basic training course for scrub nurses and circulating nurses. It consists of lectures of aseptic techniques, decontamination/sterilization methods, prevention of perioperative infections, and on-site training of scrubbing and gown techniques as well as aseptic preparation of surgical instruments in the OR. An advanced course is prepared to the experienced nurses as well. The purpose of this course is to upgrade their perioperative nursing skills so that they can demonstrate full nursing skills even in the complicated

and long operations such as transplant surgery, open-heart surgery neurosurgery and robotic surgery.

There is also a training course to medical engineers and students of biomedical engineers. This training course consists of introduction on the medical devices and electronic instruments, precautions of accidental troubles in handling surgical instruments/medical devices, development of new surgical instruments/medical devices, cardiopulmonary bypass techniques and illumination techniques in the operating fields. The contents of this course are summarized in the manual for the nursing staff and contribute to decrease the frequency of incident associated with surgical instruments and medical devices.

The on-the-job training are given to the non-nursing staff including technical officials and part-time employees since they start their careers at the surgical center. They are given lectures on aseptic techniques, sterilization/disinfection methods, prevention of perioperative infections, and maintenance of reusable surgical instruments such as forceps, scissors and clamps. These subjects are stated and summarized in the manual. Lectures are also given to the senior technical officers and part-time employees to promote their technical knowledge and skills.

12) Maintenance and management of surgical equipment

13) Nutritional management of perioperative patients

14) Others

Research Activities

- 1) Safe surgery and risk management in the OR
- 2) Improvement of cost-effectiveness in the surgical treatment
- 3) Development of central monitoring system using IT technology
- 4) Introduction of robotic surgery
- 5) Efficient use of human resources
- 6) Introduction of advanced surgical procedure including microscopy surgery and laparoscopy
- 7) Management of equipment of endoscopy-assisted surgery
- 8) Centralization of the live video images of the surgical field
- 9) Management of surgical instruments using unique device identification (UDI)
- 10) Perioperative infection control and prevention related to the sterilization
- 11) Maintenance of the surgical environment in the OR

Central Supply Service

Professor

Kazuhiko Fukatsu, M.D., Ph.D.

Lecturer

Satoshi Murakoshi, M.D., Ph.D.

Assistant Professor

Hiroshi Ookawa

※The following information is the same as that of the previous year for certain reasons.

Homepage <http://www.cc.h.u-tokyo.ac.jp/mulins/zairyobu/>

Introduction

Central supply service is an integrated place in the hospital for cleaning and sterilization of previously used devices. All re-usable devices are transported to our division via automated guided vehicle system from surgical center, ward and outpatient clinics. The used instruments are cleaned using standard precautionary procedures, disinfected, reassembled, packaged, and sterilized. The sterilized instruments are then placed at designated sites for use.

One professor and one assistant professor, one nurse, one 8 staff members, and 26 members from external staff sources are the main members of this division.

Facilities

The following facilities are located in an area of 1,077 square meters:

Cleaning equipment: 7 washer disinfectors (WDs), 1 vacuum-ultrasonic cleaning unit, 1 decompression boiling washer

Drying equipment: 5 system drying units.

Sterilizing equipment: 6 autoclaves, 1 hydrogen peroxide plasma sterilizer, 1 hydrogen peroxide sterilizer, 1 low temperature steam formaldehyde sterilizer.

Activities

Used devices are cleaned with automated washer disinfectors and/or manual washing, then packaged carefully into container sets or paper bags. The packaged materials are sterilized with autoclaves, ethylene oxide gas sterilizer or hydrogen peroxide plasma sterilizer according to their characteristics. The cleaning procedure is checked with test device. All sterilization process is recorded and ensured by chemical indicators and biological indicators. Performance validation is also carried out for autoclave sterilization.

The number of devices handled in the central supply service is dramatically increasing with increased number of operations in the surgical centers.

Staffs of central supply service have also worked for re-counting of used surgical devices on surgical center floor since 2011. The work has contributed towards risk management in the hospital.

Staffs also join infection control team round and periodically count device number in each ward for appropriate management of medical devices.

Research activities

To establish more efficient procedures for cleaning, intensive trials have been performed and the data have been presented at academic conferences. Moreover, basic research on host response to surgical

insult is another theme of our division. The research is important for improving outcome of surgical patients and our data have been published as original articles

Department of Endoscopy and Endoscopic Surgery

Associate Professor

Yousuke Nakai, M.D., Ph.D.

Assistant Professor

Naomi Kakushima, M.D., Ph.D.

Homepage <https://www.h.u-tokyo.ac.jp/patient/depts/kougaku/>

Introduction and Organization

Department of Endoscopy and Endoscopic Surgery was established in April 1997. Although the present regular staffs of our department include only two doctors, about 80 doctors from other departments including the department of gastroenterology, gastrointestinal surgery, surgical oncology, respiratory medicine, thoracic surgery, gynecologic oncology and otorhinolaryngology, perform endoscopic procedures.

Clinical activities

Endoscopic procedures, including upper gastrointestinal endoscopy, colonoscopy, bronchoscopy, otorhinolaryngological endoscopy and gynecological endoscopy, are performed from Monday to Friday. Emergency endoscopy is performed in the nighttime or holidays. The numbers of endoscopic procedures in each field are increasing gradually year by year and the total number during 2016 reached to 20,000. In the gastrointestinal tract, image enhanced endoscopy for detailed inspection and therapeutic endoscopy, including endoscopic submucosal dissection for esophageal, gastric and colorectal tumors, are major advanced fields. In addition, endoscopic diagnosis and management of pancreatobiliary diseases is also

performed. Our recent clinical activities are summarized in Table 1.

Another important activity of our department is the disinfection and maintenance of endoscopic apparatuses used in other units including the outpatient clinic, radiotherapy department, surgery department or intensive care units. Endoscopes in our hospital are collected in our department after use and disinfected.

In 2023, due to COVID-19 pandemic, prevention of COVID-19 infection both among patients and staffs has been an important topic. We will provide safe endoscopic procedures by appropriate PPE (personal protective equipment) and the social distance in the endoscopy suite.

Teaching activities

We participate in under-graduate education as a part of systemic lectures and bed-side learning by the department of gastroenterology, surgery and other departments. As for post-graduate education, training opportunities for endoscopy and endoscopic surgery are given to residents or young doctors in a program of each department. We accept foreign doctors to learn advanced endoscopic procedures.

Table1	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
EGD*	11740	11874	11944	11490	11699 (2177)	11226 (2501)	8,906	10232	10239	10030
Colonoscopy	6043	6394	6814	5921	5530 (109)	5675 (329)	4,548	5619	5445	5525
Bronchoscopy	218	228	362	350	316	395	300	312	305	292
ERCP**	1035	946	1206	1137	1057	1314	1302	1166	1326	1319
EUS†	766	882	1084	1023	923	1059	711	847	993	872
Enteroscopy	396	310	86	304	138	151	74	23	83	88
Laryngoscopy	102	105	125	114	92	102	42	39	99	93
Colposcopy	327	295	417	430	414	392	333	364	451	480
Total	20591	20627	21034	22038	20769	20169	20314	16226	18602	18699

*Esophagogastroduodenoscopy, **Endoscopic ultrasonography, †Endoscopic retrograde cholangiopancreatography, ‡performed at Center for Epidemiology and Preventive Medicine

Research activities

Our research activities cover a variety of endoscopic fields in cooperation with other departments. In the field of gastrointestinal endoscopy, our department participates in the JED (Japan Endoscopy Project) project endorsed by Japan Gastroenterological Endoscopy Society and contributes to the development of the nationwide endoscopy database.

References

1. Nakai Y, Hamada T, Saito T, Shiomi H, Maruta A, Iwashita T, Iwata K, Takenaka M, Masuda A, Matsubara S, Sato T, Mukai T, Yasuda I, Isayama H; WONDERFUL study group in Japan. Time to think prime times for treatment of necrotizing pancreatitis: Pendulum conundrum. *Dig Endosc.* 2023;35:700-710.
2. Oyama H, Hamada T, Nakai Y, Tanaka M, Endo G, Hakuta R, Ishida K, Ishigaki K, Kanai S, Kurihara K, Saito T, Sato T, Suzuki T, Suzuki Y, Takaoka S, Tange S, Tokito Y, Takahara N, Ushiku T, Fujishiro M. Clinical trajectory of intraductal papillary mucinous neoplasms progressing to pancreatic carcinomas during long-term surveillance: a prospective series of 100 carcinoma cases. *J Gastroenterol.* 2023;58:1068-1080.
3. Ishiwatari H, Kawabata T, Kawashima H, Nakai Y, Miura S, Kato H, Shiomi H, Fujimori N, Ogura T, Inatomi O, Kubota K, Fujisawa T, Takenaka M, Mori H, Noguchi K, Fujii Y, Sugiura T, Ideno N, Nakafusa T, Masamune A, Isayama H, Sasahira N. Clinical Outcomes of Inside Stents and Conventional Plastic Stents as Bridge-to-Surgery Options for Malignant Hilar Biliary Obstruction. *Dig Dis Sci.* 2023;68:1139-1147.
4. Kato H, Tateishi K, Iwadata D, Yamamoto K, Fujiwara H, Nakatsuka T, Kudo Y, Hayakawa Y, Ijichi H, Otsuka M, Kishikawa T, Takahashi R, Miyabayashi K, Nakai Y, Hirata Y, Toyoda A, Morishita S, Fujishiro M. HNF1B-driven three-dimensional chromatin structure for molecular classification in pancreatic cancers. *Cancer Sci.* 2023;114:1672-1685.
5. Hamada T, Oyama H, Nakai Y, Tange S, Arita J, Hakuta R, Ijichi H, Ishigaki K, Kanai S, Kawaguchi Y, Kogure H, Mizuno S, Saito K, Saito T, Sato T, Suzuki T, Takahara N, Tanaka M, Tateishi K, Ushiku T, Hasegawa K, Fujishiro M. Clinical Outcomes of Intraductal Papillary Mucinous Neoplasms With Dilatation of the Main Pancreatic Duct. *Clin Gastroenterol Hepatol.* 2023;21:1792-1801.
6. Hida E, Muroi K, Kakushima N, Furune S, Ishikawa E, Mizutani Y, Sawada T, Keiko M, Yamamura T, Ishikawa T, Furukawa K, Ohno E, Nakamura M, Nishida K, Fujishiro M, Kawashima H. Diagnostic Performance of Endocytoscopy for Esophageal Eosinophilia. *Digestion.* 2023;104:202-211.

7. Fukuda R, Hakuta R, Nakai Y, Hamada T, Takaoka S, Tokito Y, Suzuki Y, Oyama H, Kanai S, Noguchi K, Suzuki T, Ishigaki K, Saito K, Saito T, Takahara N, Mizuno S, Ito Y, Kogure H, Fujishiro M. Development and external validation of a nomogram for prediction of post-endoscopic retrograde cholangiopancreatography pancreatitis. *Pancreatol.* 2023;23:789-796.
8. Ishii S, Isayama H, Sasahira N, Matsubara S, Nakai Y, Fujisawa T, Tomishima K, Sasaki T, Ishigaki K, Kogure H, Okamoto T, Otsuka T, Takasaki Y, Suzuki A. A pilot study of Spring Stopper Stents: Novel partially covered self-expandable metallic stents with anti-migration properties for EUS-guided hepaticogastrostomy. *Endosc Ultrasound.* 2023;12:266-272.
9. Masugi Y, Takamatsu M, Tanaka M, Hara K, Inoue Y, Hamada T, Suzuki T, Arita J, Hirose Y, Kawaguchi Y, Nakai Y, Oba A, Sasahira N, Shimane G, Takeda T, Tateishi K, Uemura S, Fujishiro M, Hasegawa K, Kitago M, Takahashi Y, Ushiku T, Takeuchi K, Sakamoto M; GTK Pancreatic Cancer Study Group in Japan. Post-operative mortality and recurrence patterns in pancreatic cancer according to KRAS mutation and CDKN2A, p53, and SMAD4 expression. *J Pathol Clin Res.* 2023;9:339-353.
10. Kurihara K, Takahara N, Hamada T, Kanai S, Hakuta R, Nakai Y, Fujishiro M. The "zipline" technique for endoscopic removal of a migrated pancreatic stent. *Endoscopy.* 2022;55:E299-E300.
11. Saito T, Hamada T, Nakai Y. Balloon ride to WONderland: Balloon overtube-assisted transduodenal necrosectomy for walled-off pancreatic necrosis. *Dig Endosc.* 2023;35:791.
12. Sato T, Saito T, Takenaka M, Iwashita T, Shiomi H, Fujisawa T, Hayashi N, Iwata K, Maruta A, Mukai T, Masuda A, Matsubara S, Hamada T, Inoue T, Ohyama H, Kuwatani M, Kamada H, Hashimoto S, Shiratori T, Yamada R, Kogure H, Ogura T, Nakahara K, Doi S, Chinen K, Isayama H, Yasuda I, Nakai Y; WONDERFUL study group in Japan, collaborators. WONDER-01: immediate necrosectomy vs. drainage-oriented step-up approach after endoscopic ultrasound-guided drainage of walled-off necrosis-study protocol for a multicentre randomised controlled trial. *Trials.* 2023;24:352.
13. Muroi K, Kakushima N, Furukawa K, Furune S, Ito N, Hirose T, Hida E, Suzuki T, Suzuki T, Hirai K, Shibata H, Ishikawa E, Sawada T, Maeda K, Yamamura T, Ohno E, Nakamura M, Fujishiro M, Kawashima H. Novel endoscopic approaches using the endocytoscopy for the target biopsy in esophageal eosinophilia. *Esophagus.* 2023;20:325-332.
14. Hamada T, Oyama H, Nakai Y, Fujishiro M. Risk Stratification Based on Cyst Size and Its Stability for Low-Risk Intraductal Papillary Mucinous Neoplasms: Which Size Matters? *Am J Gastroenterol.* 2023;118:1705-1706.
15. Sato T, Saito T, Hamada T, Nakai Y, Fujishiro M. A release from WONderland: endoscopic ultrasonography-guided reconnection of disconnected pancreatic ducts across a walled-off necrosis cavity. *Endoscopy.* 2023;55:E82-E83.
16. Sato T, Saito T, Hamada T, Nakai Y, Fujishiro M. Rendezvous in WONderland: combined percutaneous and transluminal approach for an undrained area of massive walled-off necrosis. *Endoscopy.* 2023;55:E224-E225.
17. Mizutani S, Takahashi Y, Shimamoto T, Nakagawa H, Hisada H, Oshio K, Kubota D, Mizutani H, Ohki D, Sakaguchi Y, Yakabi S, Niimi K, Kakushima N, Tsuji Y, Wada R, Yamamichi N, Fujishiro M. Performing the ABC Method Twice for Gastric Cancer Risk Stratification: A Retrospective Study Based on Data from a Large-Scale Screening Facility. *Diagnostics (Basel).* 2023;13:1284.
18. Saito K, Michihata N, Hamada T, Jo T, Matsui H, Fushimi K, Nakai Y, Yasunaga H, Fujishiro M. Gemcitabine plus nab-paclitaxel for pancreatic cancer and interstitial lung disease: A nationwide longitudinal study. *Cancer Sci.* 2023;114:3996-4005.
19. Takahara N, Nakai Y, Ishida K, Endo G, Kurihara K, Tange S, Takaoka S, Tokito Y, Suzuki Y, Oyama H, Kanai S, Suzuki T, Sato T, Hakuta R, Ishigaki K, Saito T, Hamada T, Fujishiro M. Second Covered and Uncovered Self-Expandable Metal Stents for Recurrent

Gastric Outlet Obstruction: A Retrospective Comparative Study. *J Clin Med*. 2023;12:5241.

20. Yamagata W, Fujisawa T, Sasaki T, Ishibashi R, Saito T, Yoshida S, No S, Inoue K, Nakai Y, Sasahira N, Isayama H. Evaluation of the mechanical properties of current biliary self-expandable metallic stents: axial and radial force, and axial force zero border. *Clin Endosc*. 2023; 56:633-649.
21. Hamada T, Michihata N, Saito T, Iwashita T, Shiomi H, Takenaka M, Matsui H, Fushimi K, Isayama H, Yasuda I, Yasunaga H, Nakai Y; WONDERFUL study group in Japan and collaborators. Inverse association of hospital volume with in-hospital mortality rate of patients receiving EUS-guided interventions for pancreatic fluid collections. *Gastrointest Endosc*. 2022;98:597-606.
22. Hayashi S, Takenaka M, Kogure H, Yakushijin T, Nakai Y, Ikezawa K, Yamaguchi S, Fujisawa T, Tamaru Y, Maetani I, Maruyama H, Asai S, Takagi T, Nagaike K, Hori Y, Sumiyoshi T, Tsumura H, Doyama H, Yoshio T, Hara K, Abe S, Oda I, Kato M, Nebiki H, Mikami T, Miyazaki M, Matsunaga K, Hosono M, Nishida T; REX-GI Study Group. A follow-up questionnaire survey 2022 on radiation protection among 464 medical staff from 34 endoscopy-fluoroscopy departments in Japan. *DEN Open*. 2023;3:e227.

Department of Hemodialysis and Apheresis

Professor

Masaomi Nangaku, M.D., Ph.D.

Lecturer

Daisuke Yamada, M.D., Ph.D.

Yoshifumi Hamasaki, M.D., Ph.D.

Introduction and Organization

Hemodialysis and related blood purification therapy had been individually performed in their respective departments. However, all the departments' apparatus and human resources were centralized to form the Department of Hemodialysis and Center for Hemodialysis in 2000 at the University Hospital. The Center for Hemodialysis was further renovated and started operations in Fall of 2006. Our center is equipped with one pressure control unit in addition to 12 hemodialysis machines under a state-of-the-art hemodialysis control system. Our concept of a hemodialysis controlling system is a hub to transfer all digital and analog data from patients and to monitor machines, including blood purification machines, to the host computer in our hospital, centralizing all data and administering medical coding and billing robustly. Blood purification machines in the ICU are also connectable to this system. Blood purification machines are selected uniformly to secure patients' safety while avoiding human error and increasing the overall educational quality of staff members.

Clinical activities

1. Start of maintenance hemodialysis therapy for end-stage kidney disease (ESKD).
2. Regular hemodialysis therapy for hospitalized ESKD patients. Please note that our center does not accept holiday dialysis.
3. Emergency hemodialysis and hemodiafiltration for ICU patients.
4. Peripheral arterial disease (PAD) screening using skin reperfusion pressure examination during hemodialysis treatment, and intradialytic exercise to ameliorate frailty and sarcopenia.
5. Plasmapheresis for various pathological conditions, including neurological, dermatological, hematological, collagen diseases, TMA (TTP), and patients before and after solid organ transplantation.
6. Granulocyte and Monocyte Apheresis for inflammatory bowel diseases such as ulcerative colitis.
7. Cell-free and concentrated ascites reinfusion therapy (CART) for refractory ascites.
8. Induction and maintenance of peritoneal dialysis for ESKD.

Teaching activities

1. Tutorial course for clinical fellows applying to the speciality of blood purification therapy.
2. Exposure in hemodialysis & apheresis course to second year residents on request.
3. Our state-of-the-art blood purification protocols are summarized in Japanese handbook in 2010 [Apheresis Pocket Manual] and 2011 [CRRT Pocket Manual]. English and Chinese version of "Apheresis Pocket Manual" is available for global experts of Apheresis therapy.

4. Critical Care Nephrology Course for educating young clinical researchers and fellows in collaboration with Department of Emergency and Critical Care Medicine.

Research activities

1. Identification of prognostic factors (e.g., biomarkers in AKI/CKRT patients admitting to ICU/CCU) in patients receiving kidney replacement therapy, and epidemiological studies.
2. Associations between factors at the initiation of kidney replacement therapy and prognosis in ESKD patients.
3. Identification of prognostic factors at initiation of peritoneal dialysis (PD), and at the onset of infectious complications in PD patients.
4. Elucidation of basic mechanisms in cardio-renal syndrome and intervention.
5. Pathophysiology of acute kidney injury and its applicability for renal regenerative study.

References

1. Yoshimoto K, Matsuura R, Komaru Y, Yoshida T, Miyamoto Y, Hamasaki Y, Inokuchi R, Nangaku M, Doi K. Solute Clearance Evaluation and Filter Clotting Prediction in Continuous Renal Replacement Therapy. *J Clin Med*. 2023 Dec 15;12(24):7703.
2. Yoshida T, Matsuura R, Komaru Y, Miyamoto Y, Yoshimoto K, Hamasaki Y, Noiri E, Nangaku M, Doi K. Different Roles of Functional and Structural Renal Markers Measured at Discontinuation of Renal Replacement Therapy for Acute Kidney Injury. *Blood Purif*. 2023;52(9-10):786-792.
3. Matsuura R, Komaru Y, Hamasaki Y, Nangaku M, Doi K. BENEFIT OF HIGHER BLOOD PRESSURE TARGET IN SEVERE ACUTE KIDNEY INJURY TREATED BY CONTINUOUS RENAL REPLACEMENT THERAPY. *Shock*. 2023 Oct 1;60(4):534-538.
4. Matsuura R, Komaru Y, Miyamoto Y, Yoshida T, Yoshimoto K, Yamashita T, Hamasaki Y, Noiri E, Nangaku M, Doi K. HMGB1 Is a Prognostic Factor for Mortality in Acute Kidney Injury Requiring Renal Replacement Therapy. *Blood Purif*. 2023 Jun 19;1-8.
5. Komaru Y, Isshiki R, Matsuura R, Hamasaki Y, Nangaku M, Doi K. Application of urinary biomarkers for diagnosing acute kidney injury in critically ill patients without baseline renal function data. *J Crit Care*. 2023 Oct;77:154312.
6. Oki R, Hamasaki Y, Tsuji S, Suzuki K, Tsuneishi S, Imafuku M, Komaru Y, Miyamoto Y, Matsuura R, Doi K, Nangaku M. Clinical frailty assessment might be associated with mortality in incident dialysis patients. *Sci Rep*. 2022 Oct 21;12(1):17651.
7. Matsuura R, Honda K, Oki R, Hamasaki Y, Doi K, Nangaku M. Screening and Management for Intracranial Aneurysms in Japanese Patients With ADPKD. *Kidney Int Rep*. 2022 Jun 1;7(8):1893-1896.
8. Miyamoto Y, Iwagami M, Aso S, Uda K, Fushimi K, Hamasaki Y, Nangaku M, Yasunaga H, Doi K. Postoperative outcomes of cancer surgery in patients with and without kidney failure with dialysis therapy: a matched-pair cohort study. *Clin Kidney J*. 2022 Jan 13;15(6):1137-1143.
9. Oki R, Hamasaki Y, Komaru Y, Miyamoto Y, Matsuura R, Akari S, Nakamura T, Murase T, Doi K, Nangaku M. Plasma xanthine oxidoreductase is associated with carotid atherosclerosis in stable kidney transplant recipients. *Nephrology (Carlton)*. 2022 Apr;27(4):363-370.
10. Komai T, Iwasaki Y, Tsuchida Y, Hanata N, Tsuchiya H, Harada H, Hamasaki Y, Nangaku M, Shoda H, Fujio K. Efficacy and safety of plasma exchange in interstitial lung diseases with anti-melanoma differentiation-associated 5 gene antibody positive clinically amyopathic dermatomyositis. *Scand J Rheumatol*. 2021 Dec 13:1-7.
11. Matsuura R, Yamashita T, Hayase N, Hamasaki Y, Noiri E, Numata G, Takimoto E, Nangaku M, Doi K. Preexisting heart failure with reduced ejection fraction attenuates renal fibrosis after ischemia reperfusion via sympathetic activation. *Sci Rep*. 2021 Jul 23;11(1):15091.
12. Tomura M, Hamasaki Y, Komaru Y, Miyamoto Y, Matsuura R, Matsumoto A, Doi K, Kume H, Nangaku M. Prognostic significance of concentric

- left ventricular hypertrophy at peritoneal dialysis initiation. *BMC Nephrol.* 2021 Apr 16;22(1):135.
13. Oki R, Tsuji S, Hamasaki Y, Komaru Y, Miyamoto Y, Matsuura R, Yamada D, Doi K, Kume H, Nangaku M. Time until treatment initiation is associated with catheter survival in peritoneal dialysis-related peritonitis. *Sci Rep.* 2021 Mar 22; 11(1):6547.
 14. Oki R, Hamasaki Y, Komaru Y, Miyamoto Y, Matsuura R, Yamada D, Iwagami M, Doi K, Kume H, Nangaku M. Catheter Diversion Procedure With Exit-Site Renewal Promotes Peritoneal Dialysis Catheter Survival. *Kidney Int Rep.* 2020 Dec 7;6(2):325-332.
 15. Matsuura R, Doi K, Hamasaki Y, Nangaku M. RRT Selection for AKI Patients With Critical Illness. *Semin Nephrol.* 2020 Sep;40(5):498-505.
 16. Matsuura R, Hiraishi A, Holzman LB, Hanayama H, Harano K, Nakamura E, Hamasaki Y, Doi K, Nangaku M, Noiri E. SHROOM3, the gene associated with chronic kidney disease, affects the podocyte structure. *Sci Rep.* 2020 Dec 3;10(1): 21103.
 17. Miyamoto Y, Aso S, Iwagami M, Morita K, Fushimi K, Hamasaki Y, Nangaku M, Doi K, Yasunaga H. Expanded Indication for Recombinant Tissue Plasminogen Activator from 3 to 4.5 h after Onset of Stroke in Japan. *J Stroke Cerebrovasc Dis.* 2020 Dec;29(12):105341.
 18. Komaru Y, Doi K, Nangaku M. Urinary Neutrophil Gelatinase-Associated Lipocalin in Critically Ill Patients With Coronavirus Disease 2019. *Crit Care Explor.* 2020 Aug 20;2(8):e0181.
 19. Komaru Y, Yoshida T, Hamasaki Y, Nangaku M, Doi K. Hierarchical Clustering Analysis for Predicting 1-Year Mortality After Starting Hemodialysis. *Kidney Int Rep.* 2020 May 23;5(8): 1188-1195.
 20. Miyamoto Y, Aso S, Iwagami M, Yasunaga H, Matsui H, Fushimi K, Hamasaki Y, Nangaku M, Doi K. Association Between IV Thiamine and Mortality in Patients With Septic Shock: A Nationwide Observational Study. *Crit Care Med.* 2020 Aug;48(8):1135-1139.
 21. Matsuura R, Komaru Y, Miyamoto Y, Yoshida T, Yoshimoto K, Hamasaki Y, Nangaku M, Doi K. Different Biomarker Kinetics in Critically Ill Patients with High Lactate Levels. *Diagnostics (Basel).* 2020 Jul 4;10(7):454.
 22. Matsuura R, Iwagami M, Moriya H, Ohtake T, Hamasaki Y, Nangaku M, Doi K, Kobayashi S, Noiri E. The Clinical Course of Acute Kidney Disease after Cardiac Surgery: A Retrospective Observational Study. *Sci Rep.* 2020 Apr 16;10(1): 6490.
 23. Komaru Y, Inokuchi R, Iwagami M, Hamasaki Y, Nangaku M, Doi K. Inverse Correlation Between Incidence and Mortality of Acute Kidney Injury in Critically Ill Patients: A Systematic Review. *Shock.* 2020 Sep;54(3):280-284.
 24. Komaru Y, Doi K, Matsuura R, Yoshida T, Miyamoto Y, Yoshimoto K, Nangaku M. Urinary chloride concentration as a prognostic marker in critically ill patients. *Nephrology (Carlton).* 2020 May;25(5):384-389.
 25. Matsuura R, Iwagami M, Moriya H, Ohtake T, Hamasaki Y, Nangaku M, Doi K, Kobayashi S, Noiri E. A Simple Scoring Method for Predicting the Low Risk of Persistent Acute Kidney Injury in Critically Ill Adult Patients. *Sci Rep.* 2020 Mar 31; 10(1):5726.
 26. Miyamoto Y, Iwagami M, Aso S, Matsui H, Doi K, Yasunaga H. Pregabalin and injury: A nested case-control and case-crossover study. *Pharmacoepidemiol Drug Saf.* 2020 Feb 21.
 27. Hayase N, Doi K, Hiruma T, Matsuura R, Hamasaki Y, Noiri E, Nangaku M, Morimura N. Recombinant thrombomodulin prevents acute lung injury induced by renal ischemia-reperfusion injury. *Sci Rep.* 2020 Jan 14;10(1):289.
 28. Komaru Y, Inokuchi R, Iwagami M, Matsuura R, Hamasaki Y, Nangaku M, Doi K. Correlation between the Incidence and Attributable Mortality Fraction of Acute Kidney Injury: A Systematic Review. *Blood Purif.* 2020 Jan 22:1-8.

Immune-Mediated Diseases Therapy Center

Professor

Associate Professor

Hiroko Kanda, M.D., Ph.D.

Lecturer

Associate

Homepage <http://www.m.u-tokyo.ac.jp/patients/depts./menekishikkan/>

Introduction and Organization

In many immune diseases, some immune cells and responses are out of control. “Biologics” have been developed as agents that control the cytokines and cell surface molecules. In Japan, TNF inhibitors were introduced for the first time as “biologics” for rheumatoid arthritis (RA) in 2003. The effect of these drugs has been tremendous and has brought about a paradigm shift in RA practice, not only in terms of treatment goals, but also in terms of treatment algorithms, revised classification criteria for diagnosis, and so on. Now, “small-molecule inhibitors” that target specific molecules of intracellular signal transduction events have been added, and these drugs, called “molecular targeted therapies,” are being developed one after another. Currently, “Biologics” include 9 TNF inhibitors, 4 IL-6 inhibitors, 1 CTLA4-Ig, 6 IL-17 inhibitors, 1 IL-12/23 inhibitor, 4 IL-23 inhibitors, 2 alpha 4 integrin inhibitors, 2 IL-5 inhibitors, 1 IL-4/13 inhibitor, 1 anti-IgE antibody, 1 IL-1 inhibitor, 2 B-cell activation inhibitors, 1 type I IFN inhibitor, 2 complement activation inhibitors and 1 nFcR inhibitor, and “small-molecule inhibitors” include 5 JAK inhibitors, 1 TYK2 inhibitor and 1 PDE4 inhibitor, have been approved. Target diseases include not only

immunological diseases such as RA, juvenile idiopathic arthritis, systemic lupus erythematosus, scleroderma, adult-onset Still's disease, vasculitis, spondyloarthritis, psoriasis and psoriatic arthritis, inflammatory bowel disease, multiple sclerosis, neuromyelitis optica, nocturnal paroxysmal hemochromaturia, Castleman's disease, but also autoinflammatory diseases, atopic Dermatitis. Molecularly targeted therapies have shown high efficacy against these diseases and are expected to avoid long-term administration of corticosteroids.

In 2017, with the expansion of molecular targeted agents, the “Immune-mediated Diseases Therapy Center Outpatient Department” was established in the outpatient consultation division. Due to further increases in the number of drugs and indications, the Center was approved as a department of the Graduate School of Medicine of the University of Tokyo in April 2020. At the same time, the “Immune-mediated Diseases Therapy Center” was established on the 12th floor of Inpatient Unit B as an outpatient center to provide intravenous molecular targeted therapy for all patients with immune-mediated diseases in the university of Tokyo hospital. There are eight departments: Allergy and Rheumatology, Dermatology,

Ophthalmology, Orthopaedics surgery and Spinal surgery, Gastroenterology, Colon and Rectal surgery, Neurology, and Hematology. Together with three dedicated nurses and two pharmacists, we are working to make the outpatient clinic a smoother and safer place to provide molecular targeted therapy. In addition, once every two months, the immune-mediated diseases therapy center meeting is held as a forum for information sharing, where new drug regimens are discussed and problems are remedied.

The current number of prescriptions for molecularly targeted agents has more than doubled from 550 in 2017 to 1,800 in 2023, with 82% subcutaneous, 12% intravenous, and 6% oral. As a cross-sectional center, we would like to deepen our cooperation and aim for safer operations in the future.

Clinical activities

We have an outpatient clinic at the “Immune-Mediated Therapy Center” every Monday morning, where we provide consultation services for diagnosis and treatment of immune-mediated diseases, especially those related to molecular targeted therapy. The actual treatment is provided by the attending physician of each department, but as mentioned above, intravenous treatment is centralized at our center.

Teaching activities

As for education for outpatient staff, lectures on each disease are held once a year. When a new drug is introduced, additional lectures related to that drug are given. Medical students are educated through BSL.

Research activities

We aim to conduct research on the efficacy and safety of molecular targeted agents for each immune-mediated disease by searching for biomarkers and analyzing medical information, which will lead to the establishment of precision medicine.

References

1. Inoue M, Nagafuchi Y, Ota M, Tsuchiya H, Tateishi S, Kanda H, Fujio K. Carriers of HLA-DRB1*04:05 have a better clinical response to abatacept in rheumatoid arthritis. *Sci Rep.* 2023; 13(1); 15250.
2. Fukasawa T, Yamashita T, Enomoto A, Norimatsu Y, Toyama S, Yoshizaki-Ogawa A, Tateishi S, Kanda H, Miyagawa K, Sato S, Yoshizaki A. The optimal use of tildrakizumab in the elderly via improvement of Treg function and its preventive effect of psoriatic arthritis. *Front Immunol.* 2023 14;1286251.
3. Yamada S, Nagafuchi Y, Wang M, Ota M, Hatano H, Takeshima Y, Okubo M, Kobayashi S, Sugimori Y, Masahiro N, Yoshida R, Hanata N, Suwa Y, Tsuchida Y, Iwasaki Y, Sumitomo S, Kubo K, Shimane K, Setoguchi K, Azuma T, Kanda H, Shoda H, Zhang X, Yamamoto K, Ishigaki K, Okamura T, Fujio K.. Immunomics analysis of rheumatoid arthritis identified precursor dendritic cells as a key cell subset of treatment resistance. *Ann Rheum Dis.* 2023 82; 809-819.
4. Kanda H. Granulomatosis with polyangiitis. *Japan Medical Journal (Nihon Ijishinposha)* 5152: 44-45, 2023
5. Kanda H. Therapeutic apheresis for autoimmune and neurological diseases. *Journal of Acute Medicine/Intensive care (Sogo Igakucha)* 34; 1493-1500, 2023
6. Kanda H. Rheumatoid arthritis. *Medical Practice (Bunkodo)* 40; 280-8, 2023
7. Kanda H. IgA vasculitis. *Kidney and dialysis (Tokyo Igakusha)* 95; 229-34, 2023

Tissue Bank

Director and Associate Professor

Sumihito Tamura, M.D., Ph.D. FACS

Homepage <https://www.h.u-tokyo.ac.jp/english/centers-services/central-clinical-facilities/tissue-bank/index.html>

Introduction and Organization

The tissue bank handles cardiac arrest and brain death donor information on a 24-7-365 basis, and is responsible for the retrieval and cryo-preservation management of homograft cardiac valve and blood vessels. We provide these cryo-preserved vascular tissues to medical organizations nationwide for patients that require vascular tissue transplantation. Additionally, we initiated allograft bone banking program limited to in-house retrieval and supply since 2018. Dissemination and educational activities for the advancement of tissue transplantation and transplantation medicine is our important mission. In this line of effort, starting 2021, our staff now function as in-house organ donor coordinator.

Activities

Tissue retrieval is carried out by a team of surgeons after a transplantation coordinator certified by the Japan Society of Tissue Transplantation (JSTT) explains tissue donation to the donor's family, and obtains their consent. The donated tissue undergoes preservation work in the cleanroom located within the Central Clinical Facilities and is stored under strict round-the-clock online management, so that it may be transplanted to a patient (recipient) who is deemed to necessitate a tissue transplantation. As a rare tissue bank that handles homograft cardiac valves and vascular tissues in Japan, the department is certified by the JSTT and has the largest number of stored tissues in Japan.

Target Diseases

Cardiac valve transplantation:

Infectious endocarditis, prosthetic valve infection, aortic valve periannular abscess, some cases of congenital cardiovascular diseases (hypoplastic left heart syndrome, pulmonary artery/aorta reconstruction, etc.), etc.

Vascular transplantation

vascular prosthesis infection, infected aortic aneurysm, hepatobiliary tract and pancreas diseases, some cases of congenital cardiac diseases.

Characteristics

Excellent resistance to infections: Homograft tissues are cryopreserved in a state in which the cells are alive, and provide higher resistance to infections by bacteria than artificial cardiac valves and vessels.

No need for anticoagulation: It is not always necessary to use coagulants throughout one's life, as in the case of post-replacement of artificial cardiac valves and blood vessels, and it is particularly useful for people who are engaged with strenuous exercise, young children, or women who have a desire to give birth.

Durability: As long as 15 to 20 years. However, re-do operations may be necessary in some cases.

Banking system: In collaboration with other tissue banking facilities in Japan, responds to recovery cases mainly in the Kanto region. Certified cardiac and liver surgeons consists the donor response team. Shipment area covers entire nation.

Honoring the donor: Importance is non-comparable to artificial grafts. Human tissues are recovered from deceased donors. Since donation is rare in Japan, graft

supply remains scarce. We honor donor and family members, who decided to give to others in their final moments. It is our mission to maintain and spread this precious and important therapeutic option in Japan.

Department of Corneal Transplantation

Professor

Makoto Aihara, M.D., Ph.D.

Lecturer

Takashi Miyai, M.D., Ph.D.

※The following information is the same as that of the previous year for certain reasons.

Homepage <http://www.h.u-tokyo.ac.jp/patient/depts/kakumaku.html>

Introduction and Organization

The department of corneal transplantation was established in 1976 as one of clinical sections in the University of Tokyo Hospital. The purpose of the establishment of this section is to carry out and promote corneal transplantation and to perform clinical and basic research in the corneal diseases and corneal transplantation. The section is composed of two members (Professor Makoto Aihara, Lecturer Takashi Miyai).

Clinical activities

The clinical activities of this section include corneal transplantation and outpatient clinics for various corneal diseases as a consulting corneal service. The members are responsible not only for corneal transplantation but also for general ophthalmological practice as a senior staff member of Department of Ophthalmology, University of Tokyo. The corneal service for special cases is held every Monday (PM), Wednesday (AM), Thursday (AM), and Friday (AM). Keratoconus clinic for providing corneal crosslinking surgery, which is a brand-new treatment to halt keratoconus progression, were held in the afternoon of Thursday. Special contact lens clinic for keratoconus and post-keratoplasty eyes were in the afternoon of the second and fourth Thursday. At the corneal service, we

determine indication for corneal transplantation and follow up patients after the surgery. Total 71 corneal surgeries including keratoplasty were performed in 2021. In addition to the full-thickness corneal transplantation (penetrating keratoplasty), we have successfully performed corneal endothelial transplantation for patients with bullous keratopathy, the most common disease of corneal transplantation. Generally, corneal transplantation is performed as emergency operation, because we need to transplant corneas as soon as possible.

The other important activities of the section include mediation of donor eyes to other university hospitals and medical institutes that need donor eyes for corneal transplantation with cooperation of Eyebank. We are also performing corneal transplantation using corneas from American Eyebank as needed.

Followings are our main clinical themes to be pursued to improve the safety and prognosis of corneal transplantation.

- 1) Positive proof that donors were free of such infectious diseases as viral hepatitis, syphilis, AIDS and acute T-cell leukemia to prevent transmission to recipient patients through grafting.
- 2) Postoperative clinical outcomes are evaluated in regenerative medicine for ocular surface reconstruction, such as cultured corneal limbal, oral mucosal and conjunctival epithelial sheet

transplantation on the amniotic membrane, full-thickness corneal transplantation, lamellar keratoplasty, and endothelial keratoplasty.

- 3) Critical factors to affect clinical outcomes are statistically investigated in various kinds of corneal operation technique.

Teaching activities

We give lectures on corneal diseases and corneal transplantation to medical students and practitioners. In addition, we are engaged in practical training for young ophthalmologists on ophthalmological examinations at the outpatient clinic.

Research activities

We are conducting clinical research of postoperative results of DSAEK, clinical results of corneal crosslinking, and clinical research of corneal biometry by using anterior segment OCT.

In addition, we are investigating genetic analysis and genome editing research for corneal dystrophy. And we are also conducting research to elucidate the pathology using corneal transplant specimens.

References

- 1: Yamamoto R, Ono T, Toyono T, Shirakawa R, Noda M, Yoshida J, Miyai T. Assessment of Long-Term Anterior and Posterior Topographic Changes in the Cornea After Ptosis Surgery Using Fourier Harmonic Analysis. *Cornea*. 2021 Apr; 40(4):440-444. doi:10.1097/ICO.0000000000002429. PMID: 33881809.
- 2: Nakagawa S, Ishii H, Takamoto M, Kaburaki T, Ishii K, Miyai T. Diagnosis of cytomegalovirus corneal endotheliitis using surgically removed Descemet's membrane and endothelium despite negative results with aqueous humor PCR: a case report. *BMC Ophthalmol*. 2021 May 1;21(1):194. doi: 10.1186/s12886-021-01962-y. PMID: 33933006; PMCID: PMC8088667.
- 3: Ueda K, Ono T, Toyono T, Yoshida J, Kaburaki T, Miyai T. Descemet stripping endothelial keratoplasty after cytomegalovirus corneal endotheliitis and immunosuppression for Mooren's ulcer. *Am J Ophthalmol Case Rep*. 2021 Apr 14;22:101088. doi:10.1016/j.ajoc.2021.101088. PMID:33937582; PMCID: PMC8079431.
- 4: Omoto T, Agata C, Akiyama R, Kitamoto K, Toyono T, Yoshida J, Yamagami S, Usui T, Miyai T. Iridotrabecular and Iridocorneal Contact Changes after Cataract Surgery and Endothelial Keratoplasty in Bilateral Iridoschisis. *Case Rep Ophthalmol*. 2021 Apr 12;12(1):198-203. doi: 10.1159/000513793. PMID: 33976682; PMCID: PMC8077475.
- 5: Takahashi S, Ono T, Abe K, Mori Y, Nejima R, Iwasaki T, Miyai T, Miyata K. Prognosis and etiology of traumatic and non-traumatic corneal perforations in a tertiary referral hospital: a 30-year retrospective study. *Graefes Arch Clin Exp Ophthalmol*. 2022 Feb;260(2):629-635. doi: 10.1007/s00417-021-05389-5. Epub 2021 Sep 1. PMID: 34468830.
- 6: Ono T, Mori Y, Nejima R, Iwasaki T, Miyai T, Aihara M, Miyata K. Comparison of Corneal Irregularity After Recurrent and Primary Pterygium Surgery Using Fourier Harmonic Analysis. *Transl Vis Sci Technol*. 2021 Sep 1; 10(11):13. doi: 10.1167/tvst.10.11.13. PMID: 34515760; PMCID: PMC8444459.
- 7: Ono T, Mori Y, Nejima R, Iwasaki T, Miyai T, Miyata K. Corneal endothelial cell density and morphology in ophthalmologically healthy young individuals in Japan: An observational study of 16842 eyes. *Sci Rep*. 2021 Sep 14;11(1):18224. doi: 10.1038/s41598-021-97776-5. PMID: 34521951; PMCID: PMC8440503.
- 8: Kamiya K, Ayatsuka Y, Kato Y, Shoji N, Miyai T, Ishii H, Mori Y, Miyata K. Prediction of keratoconus progression using deep learning of anterior segment optical coherence tomography maps. *Ann Transl Med*. 2021 Aug;9(16):1287. doi: 10.21037/atm-21-1772. PMID: 34532424; PMCID: PMC8422102.
- 9: Ono T, Mori Y, Nejima R, Iwasaki T, Miyai T, Ohtani S, Miyata K. Corneal Edema with Anterior Uveitis after Exposure to the Sap of *Euphorbia trigona*: A Case Report. *Case Rep Ophthalmol*. 2021 Aug 6;12(2):699-705. doi: 10.1159/

000517742. PMID: 34594207; PMCID: PMC8436689.
- 10: Miyoshi Y, Ono T, Seki S, Toyono T, Kitamoto K, Hayashi T, Usui T, Aihara M, Miyai T. Corneal Graft Rejection after Descemet's Membrane Endothelial Keratoplasty with Peripheral Anterior Synechiae. *Case Rep Ophthalmol.* 2022 Jan 31;13(1):17-22. doi: 10.1159/000520877. PMID: 35221975; PMCID: PMC8832220.
 - 11: Ishii H, Yoshida J, Toyono T, Yamagami S, Usui T, Miyai T. Three-year results of accelerated transepithelial cross-linking (30 mW/cm² × 3 min) for keratoconus: a prospective study. *BMJ Open Ophthalmol.* 2022 Feb 8;7(1):e000827. doi: 10.1136/bmjophth-2021-000827. PMID: 35224204; PMCID: PMC8830257.
 - 12: Inamochi A, Miyai T, Usui T, Aihara M, Yamagami S. Effects of corneal epithelial superficial keratectomy in patients with focal limbal stem cell disease. *Am J Ophthalmol Case Rep.* 2021 Dec 7;25:101239. doi: 10.1016/j.ajoc.2021.101239. PMID: 34917856; PMCID: PMC8666511.
 - 13: Ono T, Takahashi S, Mori Y, Nejima R, Iwasaki T, Kataoka Y, Miyai T, Miyata K. Severe fishhook-related ocular injury: A case series. *Trauma Case Rep.* 2021 Dec 8;37:100574. doi: 10.1016/j.tcr.2021.100574. PMID: 34917740; PMCID: PMC8666537.
 - 14: Abe K, Miyai T, Toyono T, Aixinjueluo W, Inoue T, Asano S, Ishii H, Yoshida J, Shirakawa R, Usui T. Comparison of efficacy and safety of accelerated trans- epithelial crosslinking for keratoconus patients with corneas thicker and thinner than 380µm. *Curr Eye Res.* 2022 Apr; 47(4):511-516. doi: 10.1080/02713683.2021.2018466. Epub 2021 Dec 27. PMID: 34898348.

Department of Cell Therapy and Transplantation Medicine

Professor

Mineo Kurokawa, M.D., Ph.D. (Hematology-Oncology)

Assistant Professor

Moe Hidaka, M.D., Ph.D. (Pediatrics/Hematology-Oncology)

Junji Tokushige, M.D., Ph.D. (Hematology-Oncology)

Homepage <http://www.h.u-tokyo.ac.jp/mukin/>

Introduction and Organization

The Department of Cell Therapy and Transplantation Medicine was institutionally established in 1995, and was formally organized in 1996. At present, the staff consists of the above-mentioned medical doctors. Clinical facilities include 8 single-patient rooms with high-efficiency particulate air filtration and other high standards. Patients who are eligible for the treatment with high-grade infectious prophylaxis are admitted to the facilities.

Clinical activities

Approximately 1,000 patients have undergone hematopoietic stem cell transplantation (HSCT) in our department since 1995. Allogeneic bone marrow transplantation from donors Japan Marrow Donor Program (JMDP) as well as international bone marrow donor programs, HSCT from HLA-mismatched donors, and donor lymphocyte infusion are available. In 2022, 17 patients (including 2 children) received autologous HSCT and 23 patients (including 5 children) allogeneic HSCT. We cooperate with the members of Department of Hematology and Oncology, Hematology/Oncology group in the Department of Pediatrics, and Department of Transfusion Medicine.

Allogeneic hematopoietic stem cell transplantation: Bone marrow cells are operatively harvested and infused without preservation. For peripheral blood

stem cell transplantation, leukapheresis is performed with the use of an automated continuous flow blood cell separator, and harvested cells are preserved at -196°C in cooperation with Department of Transfusion Medicine. Recently, transplantation after pre-conditioning of reduced intensity (RIST for reduced-intensity HSCT or NST for non-myeloablative HSCT) is commonly performed for the elderly and patients with organ dysfunction. The development of this strategy is expanding the eligibility of transplant recipients.

Some patients cannot get transplantation treatment because they don't have eligible donors with at least a 90% match of HLA. Recently, with the development of new methods of transplantation management, such as immunosuppression, it has become possible to safely carry out transplants from donors with a 50% HLA match (HLA haploidentical transplantation; haplo transplants), and the procedure is expected to spread more widely in the future. The department proactively performs haplo transplants for patients in need to overcome diseases.

Allogeneic HSCT for the elderly and HLA haploidentical transplantation are performed under the admission of Patient Relations and Clinical Ethics Center.

High-dose chemotherapy with or without autologous stem cell support: High-dose chemotherapy is administered according to the malignant disease. For

the autologous stem cell support, peripheral blood stem cell is usually selected as a source of stem cells. Similar procedures used in the allogeneic stem cell harvest are performed for leukapheresis and preservation of autologous stem cell. Malignant lymphomas arising from the central nervous system (brain and spinal cord) are known to be refractory to treatment and have a poor prognosis. Recently, chemotherapy including autologous HSCT has been used to treat this disease with good efficacy. In our department, we are striving to improve the prognosis of patients with CNS malignant lymphoma by providing treatment including autologous transplantation.

CAR-T Cell Therapy: CAR-T cell therapies are customized for each individual patient. They are made by collecting T cells from the patient and re-engineering them in the laboratory to produce proteins on their surface called chimeric antigen receptors, or CARs. The CARs recognize and bind to specific proteins, or antigens, on the surface of tumor cells, and allow T cells to exert their ability to kill these tumor cells. By collaborating with the Department of Hematology and Oncology, the Department of Pediatrics (Hematology/Oncology), and the Cell Processing Center, we are performing this most advanced and promising cancer treatment for patients with hematologic malignancies, and actively recruiting patients.

Clinical conference for hematopoietic stem cell transplantation: The conference is held monthly. The members of Department of Hematology and Oncology, Hematology/Oncology group in Department of Pediatrics, and Department of Transfusion Medicine join the conference and discuss on HSCT recipients.

Teaching activities

Together with the members of Department of Hematology and Oncology and Hematology/Oncology group in the Department of Pediatrics, lecture courses on etiology, pathogenesis, clinical and laboratory features, differential diagnosis, therapy and prognosis for all hematological diseases are provided to the second-grade medical students. Clinical clerkship courses are given to the third-grade medical students,

who join the patient care teams consisting of junior and senior medical doctors and learn medical practices and patient management, through playing a role as a junior member of the team, as well as through discussions and presentations. We also provide educational opportunities to continuously develop future specialists on HSCT – Board-certified physicians, hematopoietic cell transplant coordinators, and long-term follow up nurses by the Japan Society for Hematopoietic Cell Transplantation.

Research activities

The major research projects are focused on clinical studies such as development of improved/new methods for hematopoietic stem cell transplantation, immunotherapy for hematopoietic malignancies, and basic studies on hematopoietic stem cells, leukemogenesis and regenerative medicine using hematopoietic cells. In the area of pediatric oncology, we continue the studies on molecular mechanisms of pediatric malignancies such as neuroblastoma, rhabdomyosarcoma, and infant leukemia.

References

1. Oyama T, Matsuda K, Honda A, Maki H, Masamoto Y, Murakami D, Toya T, Sakurai M, Kataoka K, Doki N, and Kurokawa M. Clinical characteristics of steroid-responsive but dependent chronic graft-versus-host disease: a multicenter retrospective analysis. *International Journal of Hematology* 117(2): 260-268, 2023.
2. Kanda Y, Usuki K, Inagaki M, Ohta A, Ogasawara Y, Obara N, Kako S, Kurokawa M, Shimada N, Suzuki T, Hama A, Yamaguchi H, Nakao S, and Yamazaki H. Decision analysis of allogeneic bone marrow transplantation versus immunosuppressive therapy for young adult patients with aplastic anemia. *International Journal of Hematology* 117(5): 660-668, 2023.
3. Yoshida M, Matsuda K, Taoka K, Honda A, Maki H, Masamoto Y, Jona M, Nishikawa M, Yatomi Y, and Kurokawa M. Expansion of large granular lymphocytes after autologous hematopoietic stem cell transplantation. *International Journal of Hematology* 117(6): 839-844, 2023.
4. Mitsutake A, Iwata A, Ishiura H, Mitsui J, Mori H,

Toya T, Honda A, Kurokawa M, Sakai N, Tsuji S, and Toda T. Favorable outcome of hematopoietic stem cell transplantation in late-onset Krabbe disease. *Brain and Development* 45(7): 408-412, 2023.

Clinical Nutrition Center

Head of the Center

Kazuhiko Fukatsu (Professor)

Assistant Head of the Center

Naoto Kubota (Associate Professor) Department of Clinical Nutrition Therapy

Hideaki Ijichi (Lecturer) Division of Dietary Treatment and Nutritional Care

Homepage <http://www.h.u-tokyo.ac.jp/patient/depts/eiyou/>

Introduction and Organization

In 1922, a stall in the outpatient department of the hospital and hospital ward shop sold milk, baked goods, cider and ice cream. In 1925, a service contract between the hospital and the Kojinkai Foundation resulted in the start of a patient food service. In 1936, a “special therapeutic diet” approach for newborn infants, diabetes, nephropathy in which a physician prescribed the food composition individually for each patient was instituted for the first time in Japan. In 1950, a national-hospital complete food service system was announced, and the nutrient content provided was standardized. The nutrient content provision for patient meals at the time was 2400 kcal/day. In 1952, the inpatient meal service was officially outsourced to a foundation.

In 1957, the first nationwide meeting of national-university-hospital head dietitians was held at the University of Tokyo with the aim of improving patients’ diets.

In 1958, the complete food service was abolished. Implementation of a standard food service and staffing with a dietitian became required conditions, and the food service section was staffed by a part-time section chief and a dietitian. In 1962, a request from the nationwide meeting of national-university-hospital head dietitians, which primarily conducted its activities at the University of Tokyo, was realized, and the managerial dietitian system was established by a partial revision of the Nutritionists Act. In 1972, nutritional guidance was actively provided to inpatients and outpatients with the aim of obtaining approval to

charge fees, and in 1978 a medical diet charge and nutrition guidance charge were established. In 1988, a timely tray service achieved by using hot and cold food-tray carts was instituted.

In 1991, the name of the food service section was changed to the “Department of Nutrition Management”. At the same time, the nutrition sections of the main hospital and branch hospital were consolidated, and the head of the Department of Nutrition Management, who was a managerial dietitian, assumed the section manager post to form a system composed of 5 managerial dietitians at the main hospital and 3 managerial dietitians at the branch hospital.

In 1994, a diet therapy notification system on admission was set up. An on-admission nutrition guidance fee was also established.

In 1998, the first Diet Therapy Exhibit organized by the Department of Nutrition Management was conducted as part of the diabetes week events by the Tokyo Diabetes Association. Since then, Diet Therapy Exhibit has been conducted every year for over 20 years.

In 2001, integration of the branch hospital with the main hospital resulted in an 8-managerial-dietitian system. In 2004, the Department of Nutrition Management was separated from the medical service division. In 2005, the introduction of the self-pay system for inpatient meals meant that inpatients began to be charged for their meals. During the same year one managerial dietitian (limited-term employment) was added to the staff.

In 2006, charges for the performance of nutrition management were newly established, and that meant

providing nutrition management for all patients. The increase in work was accompanied by the addition of one managerial dietitian (limited-term employment) to the staff. Team care was introduced the same year, and in-hospital activity in the form of an all-department nutrition support team (NST) was inaugurated. Each hospital ward was staffed with a physician, managerial dietitian, and nurse in charge of an NST, and whenever necessary members from other fields (pharmacists, medical technologists, physical therapists) joined, and they held a hospital ward meeting once a week. In 2010, an NST committee was created as a result of the establishment of charges for NSTs. The NST director up until that time became a member of the committee and played an active role as the center of in-hospital NST activities. The addition of one managerial dietitian (full time) was approved as a full-time employee to engage in the activities of charges for the NST. In 2011, the inauguration of a nutritional guidance service for recipients of health checkups in the Department of Epidemiology and Preventive Medicine was accompanied by the addition of one managerial dietitian (limited-term employment) to the staff. In 2012, charges for conducting nutrition management were abolished. They were incorporated into the basic hospital-admission fee, and the nutrition management system by physicians, managerial dietitians, and nurses was improved.

In 2013, the Department of Nutrition Management was reorganized as the Department of Clinical Nutrition Therapy. A physician (Professor, the head of the Central Clinical Services Administration) assumed the concurrent post of head of the Department, and the head of the Department of Nutrition Management assumed the post of Assistant Head of the Department; they undertook responsibility for managing the food service, maintaining activities of the NST, and strengthening its functions. In 2014, two physicians, full-time department head (associate professor) and lecturer, were assigned and improvements were made to NST activities and to the nutrition therapy, education, and research system. As a result of a managerial strategic personnel distribution, 5 new managerial dietitians (full-time) have also been assigned this fiscal year. Along with the increase in work of managerial dietitians for strengthening the nutrition management system and expanding the number of clinical trials in

P1 unit, another managerial dietitian (limited-term employment) was added to the staff in May 2015.

Long-coveted introduction of the New Cook Chill System was eventually admitted by the University of Tokyo and the process was started in October 2016. Renovation of the main kitchen was started in June 2017. During the renovation, the makeshift kitchen was placed on the 1st floor (the main kitchen) and the 3rd basement floor (the washing room and the formula room) of the Inpatients Ward A and the menu was restricted for the makeshift kitchen use. In February 2018, the New Cook Chill System in the University of Tokyo Hospital began. The menu was considerably modified for the new cooking system.

In April 2018, a new formula room was launched on the first floor of the Inpatients Ward A for the expansion of Pediatric Medical Center. Monthly issue of diet news for the patients started in June 2018 and Grand Menu for the special admission room was newly set up in January 2019.

In 2019, the University of Tokyo Hospital was recognized as Tokyo Food Hygiene Meister by Tokyo Metropolitan Certification System for Self-Management of Food Hygiene, and also as an Elite Institution of Food Hygiene by Bunkyo-ku.

In April 2020, the department was reorganized to be the Clinical Nutrition Center, composed of the Department of Clinical Nutrition Therapy in charge of nutritional guidance and the Division of Dietary Treatment and Nutritional Care in charge of meal service and nutritional care for inpatients. A professor of the Surgical Center assumed the Head of the Clinical Nutrition Center, and the both sections named a director (physician) and a deputy director (managerial dietitian), respectively. All the other managerial dietitians belong to the Center and engage in the works of both sections.

During the pandemic of COVID-19, the hospital closed the special admission room and the Grand Menu was stopped in 2021. Several changes were added for promoting the efficiency in the food service operation during 2020-2022, then the deputy director of Division of Dietary Treatment and Nutritional Care, a temporary appointment, was discontinued in 2023.

Clinical Activities

The Center is proactively conducting nutritional guidance in regard to metabolic diseases, including diabetes, chronic kidney disease, dyslipidemia, and obesity, perioperative guidance, including in regard to postgastrectomy diets, hepatobiliary and pancreatic disease diets, and cardiac disease diets, etc.

In 2023, nutritional guidance of inpatients and outpatients increased upto 4609 instances for inpatients and 6998 instances for outpatients. Nutritional guidance for malignant tumor patients was performed for 1794 instances.

The Center is also proactively cooperating with several departments in the hospital. In 2023, dietary management with palliative care was 642 instances, nutritional guidance for outpatient chemotherapy was 229 instances, nutritional guidance at the preventive medicine center was 57 instances, nutritional guidance at the international preventive medicine center was 109 instances. In addition, the provision of inpatient nutrition information was 127 instances.

In April 2014, the department started calculating charges for NST and counted 1261 instances in the first fiscal year. In April 2016, dentists joined the NST round and started to calculate the additional charge. After 2020, due to the COVID-19 pandemic, the instances decreased. 252 rounds were performed and 157 instances were calculated in 2023.

In November 2014, a procedure manual of nutritional management was revised and an original two-step nutritional screening by physicians, managerial dietitians, nurses and pharmacists was introduced. In this system, the high-risk patients of malnutrition were weekly screened through the common criteria in our hospital and referred to the NST of each floor (ward NST). In April 2015, alternative initial screening criteria specific for pediatric and pregnant patients were added to the procedure manual of nutritional management, respectively. By 2019, almost all the floor started the ward NST, which indicated raised awareness of nutritional care as a team medicine in our hospital. Then, in 2020, instead of the common screening criteria, each floor started more specific screening for the ward NST, based on the characteristics of the patients and treatment department.

In 2018, related with the start of surgery for severe

obesity patients (sleeve gastrectomy), sleeve diet was newly introduced. In January 2019, ketogenic diet was also introduced in cooperation with Epilepsy Center.

In 2019, in addition to the Tokyo Food Hygiene Meister and Elite Institution of Food Hygiene by Bunkyo-ku, the safe and assured food service in our hospital was evaluated “S” rank (the highest) by the hospital function evaluation.

Educational Activities

The department has accepted managerial dietitian clinical trainees. In 2019, the department accepted 45 trainees from 7 training schools: Ochanomizu University, Tokyo Kasei University, Otsuma Women's University, Kagawa Education Institute of Nutrition, Jissen Women's Educational Institute, Japan Women's University, and Wayo Women's University.

In 2011, the department began accepting NST trainees. From 1 to 4 or 5 terms are conducted a year (5 days/ week/ term). Participants are mainly managerial dietitians, pharmacists, nurses, medical technologists, and physical therapists, and candidates are trainees whose aim is acquiring the qualifications certified by academic societies or to become a full-time employee to calculate the billing charges for the NST. There were 18 participants in 2019. During the COVID-19 pandemic, these programs accepting external trainee have been stopped.

In 2017, the department was involved in the curriculum of Clinical Clerkship 2, the medical education program of the Faculty of Medicine, the University of Tokyo. 112 medical students at the 6th grade participated in the two-day practice course in 2023.

To disseminate NST activities fully in the hospital, the department has organized two NST-related seminars throughout the year: Basic Series for Nutrition Therapy and Clinical Nutrition Seminar. The department has also organized NST Conference and Joint Conference of Team Medicine (JCTM) for case discussions to facilitate cooperation with each floor NST and other medical teams. In 2020, due to the COVID-19 pandemic, all the seminars and JCTM were conducted online and the NST Conference was adjourned. In 2021, the Center combined the two seminars and restarted with a hybrid style, on-site and online. In 2023, 20 seminars were given to total 640

attendee.

In 2015, the department started “Nutritional Management e-learning” for all employee to learn basic knowledge of nutritional management procedure.

In 2016, “The Manual of The Department of Clinical Nutrition Therapy 2015-2016” was published. After that, “The Pocket Manual of The Department of Clinical Nutrition Therapy 2016-2017”, “The Manual of The Department of Clinical Nutrition Therapy 2017-2019”, “Records of the Kitchen Renovation 2016-2018”, “The Pocket Manual of The Department of Clinical Nutrition Therapy 2018-2021”, “Illustrated Tools of Nutritional Guidance 2018-2022” and “New Cook Chill Manual 2018-2022” were published by March 2020.

Research

- Research topic: “Retrospective study using database of patients records who have undergone nutritional guidance”
- Research topic: “Surveillance of nutritional status and its change in pancreatic cancer patients receiving chemotherapy”
- Research topic: “Surveillance of change in body composition by using visceral fat measuring device”
- Research topic: “Roles of microbiome in lifestyle-related diseases” (Joint research)
- Research topic: “Exploratory research in the association of plasma amino acids and the nutrition status of patients with diabetes mellitus and the comorbidities”
- Research topic: “Exploratory research of biomarkers in the blood and body fluid for diabetes mellitus”
- Research topic: “Impact of periodical measurement of serum glycoalbumin on the patients with diabetes mellitus”
- Research topic: “Impact of periodical measurement of diabetes mellitus-related biomarkers in tear fluid”
- Research topic: “Association of food diversity and obesity in patients with diabetes mellitus”
- Research topic: “Evaluation of nutritional guidance on the treatment-naïve patients with high LDL-cholesterolemia”
- Research topic: “Association of initial nutritional condition and prognosis in elderly patients at NST round”
- Research topic: “Assessment of dietary intake of inpatients with diabetes mellitus”
- Research topics: “Correlation research of biomarkers in the blood and body fluid and diabetes mellitus”
- Research topic: “Association of diet and nutritional factors and control of blood sugar and lipid in patients with diabetes mellitus”
- Research topic: “Association of diet and nutritional factors and sarcopenia and frail in elderly patients with diabetes mellitus”
- Research topic: “Association of dietary intake and background dietary habit in inpatients with diabetes mellitus”
- Research topic: “Assessment of dietary intake and bodily characteristics in patients with eating disorder”
- Research topic: “Association of change of dietary intake and weight loss effect in highly obese patients after bariatric surgery”
- Research topic: “Surveillance of nutritional status and its change in patients with severe heart failure”
- Research topic: “Surveillance of nutritional assessment and guidance at the perioperative clinic”

References

<Publications (English)>

1. Seimiya T, Suzuki T, Iwata T, Kishikawa T, Sekiba K, Shibata C, Ishigaki K, Fujiwara H, Oyama H, Kanai S, Sato T, Nakai Y, Ishibashi R, Moriyama M, Nakagawa R, Ijichi H, Otsuka M, Koike K. Combination of serum human satellite RNA and miR-21-5p levels as a biomarker for pancreatic cancer. *iScience*. 26:106021, 2023.
2. Takahashi K, Higashizono K, Fukatsu K, Murakoshi S, Takayama H, Noguchi M, Matsumoto N, Seto Y. Prehabilitation Ameliorates Gut Ischemia Reperfusion Injury in Mice. *J Surg Res*. 282:71-83, 2023.
3. Sawada M, Ohkuma K, Aihara M, Doi S, Sekine R, Kaneko T, Iimuro S, Ichi I, Usami S, Ohe K, Yamauchi T, Kubota N. Impact of the COVID-19 pandemic on the glycemic control, eating habits, and body compositions of people with diabetes mellitus: A retrospective longitudinal observational study. *J Diabetes Investig*. 14:321-328, 2023.
4. Aihara M, Irie T, Yasukawa K, Minoura I, Miyauchi N, Nishi M, Katayama N, Yachiku K,

- Jinnouchi H, Kadowaki T, Yamauchi T, Yatomi Y, Kubota N, Sekimizu K. Development of a high-performance liquid chromatographic glycosylated albumin assay using finger-prick blood samples. *Clin Chim Acta* 542:117272, 2023.
5. Ijichi H. Significance of Tumor Microenvironment for Regulating Pancreatic Cancer. *Cancers (Basel)*. 15:2482, 2023.
6. Kato H, Tateishi K, Iwadata D, Yamamoto K, Fujiwara H, Nakatsuka T, Kudo Y, Hayakawa Y, Ijichi H, Otsuka M, Kishikawa T, Takahashi R, Miyabayashi K, Nakai Y, Hirata Y, Toyoda A, Morishita S, Fujishiro M. HNF1B-driven three-dimensional chromatin structure for molecular classification in pancreatic cancers. *Cancer Sci*. 114:1672-1685, 2023.
7. Aihara M, Jinnouchi H, Yoshida A, Ijima H, Sakurai Y, Hayashi T, Koizumi C, Kubota T, Usami S, Yamauchi T, Sakata T, Kadowaki T, Kubota N. Evaluation of glycosylated albumin levels in tears and saliva as a marker in patients with diabetes mellitus. *Diabetes Res Clin Pract*. 199:110637, 2023.
8. Hayashi T, Wada N, Kubota T, Koizumi C, Sakurai Y, Aihara M, Usami S, Yamauchi T, Kubota N. Associations of sleep quality with the skeletal muscle strength in patients with type 2 diabetes with poor glycemic control. *J Diabetes Investig*. 14:801-810, 2023.
9. Hamada T, Oyama H, Nakai Y, Tange S, Arita J, Hakuta R, Ijichi H, Ishigaki K, Kanai S, Kawaguchi Y, Kogure H, Mizuno S, Saito K, Saito T, Sato T, Suzuki T, Takahara N, Tanaka M, Tateishi K, Ushiku T, Hasegawa K, Fujishiro M. Clinical Outcomes of Intraductal Papillary Mucinous Neoplasms With Dilatation of the Main Pancreatic Duct. *Clin Gastroenterol Hepatol*. 21:1792-1801, 2023.
10. Itaya T, Sano M, Kajiwaru I, Oshima Y, Kuramochi T, Kim J, Ichimaru Y, Kitajima O, Masamune A, Ijichi H, Ishii Y, Suzuki T. Mirogabalin improves cancer-associated pain but increases the risk of malignancy in mice with pancreatic cancer. *Pain*. 164:1545-1554, 2023.
11. Hiraike Y, Saito K, Oguchi M, Wada T, Toda G, Tsutsumi S, Bando K, Sagawa J, Nagano G, Ohno H, Kubota N, Kubota T, Aburatani H, Kadowaki T, Waki H, Yanagimoto S, Yamauchi T. NFIA in adipocytes reciprocally regulates mitochondrial and inflammatory gene program to improve glucose homeostasis. *Proc Natl Acad Sci U S A*. 120:e2308750120, 2023.
12. Ohkuma K, Sawada M, Aihara M, Doi S, Sekine R, Usami S, Ohe K, Kubota N, Yamauchi T. Impact of the COVID-19 pandemic on the glycemic control in people with diabetes mellitus: A retrospective cohort study. *J Diabetes Investig*. 14:985-993, 2023.
13. Takeuchi T, Kubota T, Nakanishi Y, Tsugawa H, Suda W, Kwon AT, Yazaki J, Ikeda K, Nemoto S, Mochizuki Y, Kitami T, Yugi K, Mizuno Y, Yamamichi N, Yamazaki T, Takamoto I, Kubota N, Kadowaki T, Arner E, Carninci P, Ohara O, Arita M, Hattori M, Koyasu S, Ohno H. Gut microbial carbohydrate metabolism contributes to insulin resistance. *Nature*. 621:389-395, 2023.
14. Matsukawa T, Yagi T, Uchida T, Sakai M, Mitsushima M, Naganuma T, Yano H, Inaba Y, Inoue H, Yanagida K, Uematsu M, Nakao K, Nakao H, Aiba A, Nagashima Y, Kubota T, Kubota N, Izumida Y, Yahagi N, Unoki-Kubota H, Kaburagi Y, Asahara SI, Kido Y, Shindou H, Itoh M, Ogawa Y, Minami S, Terauchi Y, Tobe K, Ueki K, Kasuga M, Matsumoto M. Hepatic FASN deficiency differentially affects nonalcoholic fatty liver disease and diabetes in mouse obesity models. *JCI Insight*. 8:e161282, 2023.
15. Yoshida Y, Doi T, Oka H, Kato S, Ohtomo N, Nakamoto H, Takeda N, Inuzuka R, Yagi H, Oshima Y, Tanaka S, Fukatsu K, Taniguchi Y. Reduced volume and altered composition of paraspinal muscles in Marfan syndrome: A retrospective cohort study. *Medicine (Baltimore)*. 102:e35382, 2023.
16. Sano T, Ochiai T, Nagayama T, Nakamura A, Kubota N, Kadowaki T, Wakabayashi T, Iwatsubo T. Genetic Reduction of Insulin Signaling Mitigates Amyloid- β Deposition by Promoting Expression of Extracellular Matrix Proteins in the Brain. *J Neurosci*. 43:7226-7241, 2023.
17. Soeda K, Sasako T, Enoku K, Kubota N, Kobayashi N, Ikushima YM, Awazawa M, Bouchi R, Toda G, Yamada T, Nakatsuka T, Tateishi R, Kakiuchi M, Yamamoto S, Tatsuno K, Atarashi K,

- Suda W, Honda K, Aburatani H, Yamauchi T, Fujishiro M, Noda T, Koike K, Kadowaki T, Ueki K. Gut insulin action protects from hepatocarcinogenesis in diabetic mice comorbid with nonalcoholic steatohepatitis. *Nat Commun.* 14:6584, 2023.
18. Hasegawa Y, Yoshida M, Minematsu T, Sugama J, Sanada H. The reliability and validity of visually assessing temporal wasting in older adults. *Kango Rikokai Zasshi.* 11:37-46, 2023.
19. Hasegawa Y, Yoshida M, Minematsu T, Hattori N, Sanada H. Nutritional management using ultrasonography of the temporal muscle for patients with pressure injuries in a home care setting: a case report. *Nihon Soshou Ostomy Shikkin Kanri Gakkaishi.* 26:384-390, 2023.

Swallowing Center

Director/Associate Professor

Rumi Ueha, M.D., Ph.D.

Vice Director

Haruhi Inokuchi, M.D., Ph.D. (Department of Rehabilitation Medicine)

Asako Kaneoka, SLP., Ph.D. (Rehabilitation Center)

Homepage <http://www.m.u-tokyo.ac.jp/mcm/>

Introduction and Organization

A condition in which there is a problem with swallowing food or drink is called swallowing disorder. In recent years, advances in medical technology have increased the lifesaving rate and aging of society, resulting in an increase in the number of patients with dysphagia among a wide range of age groups caused by congenital diseases, stroke, intractable diseases, malignant tumors, and aging. Since 2009, we have been providing medical care for patients with dysphagia at the University of Tokyo Hospital by organizing the "Swallowing Support Team" with specialists in the field of swallowing. To provide a more specialized and multifaceted treatment for dysphagia in 2021, the Swallowing Center was established.

At the Swallowing Center, the departments of Otolaryngology and Head and Neck Surgery, Rehabilitation Medicine, Oral-Maxillofacial Surgery and Orthodontics, Geriatric Medicine, Pediatrics, Pediatric Surgery, Neurology, Clinical Nutrition, Nursing, and Clinical Laboratory work together as a team of multidisciplinary specialists, including physicians, speech pathologists, nurses, dietitians, pharmacists, and dental hygienists, taking a multifaceted approach to each patient.

The following is a list of departments and divisions that collaborate with the Swallowing Center:

1. Otolaryngology and Head and Neck Surgery
2. Rehabilitation Medicine
3. Oral-Maxillofacial Surgery and Orthodontics
4. Geriatric Medicine

5. Pediatrics
6. Pediatric Surgery
7. Neurology
8. Clinical Nutrition Center
9. Nursing Department
10. Pharmaceutical Department

We also hold a bimonthly meeting of the Swallowing Center to share information and improve problems.

Clinical activities

We have outpatient clinics for patients with dysphagia at the Department of Otorhinolaryngology and Head and Neck Surgery every Tuesday and Thursday morning. For hospitalized patients, we provide more specialized and multifaceted treatment for dysphagia caused by a variety of factors in a wide range of age groups, with physicians and specialists from multiple departments working as a team. A weekly swallowing conference is held on Tuesdays to discuss the various cases with a multidisciplinary team.

We also actively perform surgical treatment for dysphagia (to prevent aspiration or to improve swallowing function) and provide intensive rehabilitation after surgery to improve swallowing function during hospitalization.

The following is a list of swallowing examinations performed in 2023:

- Videofluorographic swallowing study: 695 cases
- Videoendoscopic examination of swallowing: 605 cases
- High-resolution swallowing manometry: 48 cases

- Swallowing computed tomography: 13 cases

Teaching activities

The center emphasizes educational activities on feeding and swallowing throughout the hospital, and actively organizes e-learning and training sessions. The e-learning materials are updated every year. Documents and educational content concerning feeding and swallowing are made available on the hospital's internal website, ensuring accessibility throughout the facility.

We participate in undergraduate education as part of systemic lectures and bedside learning by the Department of Otolaryngology and Head and Neck Surgery and Rehabilitation Medicine.

Since 2022, we have been proactively accepting international observers and clinical fellows, annually providing opportunities for several overseas doctors to engage in clinical practice.

Research activities

Our research field covers a variety of topics related to swallowing. Clinical and basic research activities are highly encouraged. Clinical research is related to swallowing dynamics and physiology, laryngology, broncho-esophagology, and rhinology, as well as case research and clinical statistics.

Basic research is also encouraged to solve the essence of clinical problems and to elucidate basic phenomena or anatomical and cellular structures. Our research topics are as follows:

- Effects of aspiration prevention surgery on patients with severe dysphagia
- Swallowing mechanisms using pathological and electrophysiological analysis and VR system
- Esophageal Motility in neuromuscular disorders
- Esophageal Motility in systemic sclerosis
- Swallowing impairment in patients with lung transplants
- Evaluation of swallowing physiology with pharyngo-esophageal high-resolution manometry
- Regeneration of vocal fold structure and its molecular mechanism
- Gene expression analysis of recurrent respiratory papillomatosis
- Research on preventive rehabilitation for dysphagia due to chemoradiotherapy for head and neck cancer
- Pathophysiology of dysphagia after esophageal cancer surgery
- Statistical analysis of dysphagia patients using big data
- Research on the effect of cervical spine surgery on swallowing function

References

- Suto A, Ueha R, Ogura T, Maeda E, Tatebayashi M, Shimada D, Koyama M, Sato T, Goto T, Yamauchi A, Yamasoba T. Swallowing computed tomography and virtual reality as novel imaging modalities for the diagnosis of clicking larynx: two case reports. *Auris Nasus Larynx*. 50:468-472. 2023.
- Koyama M, Ueha R, Sato T, Goto T, Yamauchi A, Kaneoka A, Suzuki S, Nito T, Yamasoba T. Aspiration prevention surgery: clinical features, improvement of oral intake and suction frequency. *Otolaryngol Head Neck Surg*. 168: 1146-1155, 2023.
- Koyama S, Mori E, Ueha R. Insight into the mechanisms of olfactory dysfunction by COVID-19. *Auris Nasus Larynx*. 50(4):490-498, 2023.
- Kaneoka A, Ogino A, Inokuchi H, Shichiri T, Matsuzaki A, Sato T, Goto T, Yamauchi A, Saito Y, Ueha R. The use of a patient booklet to enhance adherence to prophylactic exercises for patients undergoing chemoradiation therapy for head and neck cancer. *The Japan Society of Logopedics and Phoniatrics*. 64:85-95, 2023.
- Ueha R, Magdayao BR, Koyama M, Sato T, Goto T, Yamasoba T. Aspiration prevention surgeries: a review. *Respir Res*, 24(1):43, 2023.
- Inamoto Y, Ueha R, Fernandez GM. Emerging Dysphagia Technologies: Swallowing CT. *Curr Otorhinolaryngol Rep*, 11: 154-160, 2023.
- Goto T, Ueha R, Sato T, Yamasoba T. Effects of Early Local Administration of High-dose bFGF on a Recurrent Laryngeal Nerve Injury Model. *J Otolaryngol Head Neck Surg*, 52(1):47, 2023.
- Hara M, Ueha R, Sato T, Goto T, Yoshizaki A, Sumida H, Sato S, Yamasoba T. Clinical risk

factors for dysphagia and esophageal dysmotility in systemic sclerosis. *J Clin Med*, 12(10):3448, 2023.

9. Ueha R, Cotaoco C, Kondo K, Yamasoba T. Management and treatment for dysphagia in neurodegenerative disorders. *J Clin Med*, 13(1): 156, 2023.
10. Kaneoka A, Inokuchi H, Ueha R, Sato T, Goto T, Yamauchi A, Seto Y, Haga N: Longitudinal Analysis of Dysphagia and Factors Related to Postoperative Pneumonia in Patients Undergoing Esophagectomy for Esophageal Cancer. *Dysphagia*, 39(3):376-38, 2023.
11. Konishi T, Inokuchi H, Yasunaga H. Services in public long-term care insurance in Japan. *Ann Clin Epidemiol*, 6(1):1-4, 2023.
12. Konishi T, Sakata A, Inokuchi H, Kumazawa R, Matsui H, Fushimi K, Tanabe M, Seto Y, Yasunaga H. Treatments and outcomes of adult parapharyngeal and retropharyngeal abscess: 1882 cases from a Japanese nationwide database. *Am J Otolaryngol*, 44(2):103770, 2023.

International Medical Center

Director and Associate Professor

Sumihito Tamura, M.D., Ph.D. FACS

Homepage <http://www.h.u-tokyo.ac.jp/english/international-patients/index.html>

Introduction and Organization

The International Medical Center is a Division within the Central Clinical Facilities established to enhance The University of Tokyo Hospital's development as an international medical hub in coordination with the University of Tokyo's significant movement in globalization. Designated management position has been assigned.

Activities and challenges

The University of Tokyo Hospital offers sophisticated surgery and state-of-the-art treatment in variety of fields. One of the roles of the International Medical Center is to establish a system through which we provide medical expertise to patients from overseas. The International Medical Center will cater to the various requirements that must be met when accepting overseas patients, including multilingual support, translation of medical documents, and offering solutions to financial challenges, so that each department can focus solely on providing medical treatment to those patients.

As well as receiving patients, another important aspect is the globalization of clinical education. We hope to establish a system in which non-Japanese doctors accepted for residencies, or those who come to receive cutting-edge medical training can carry out operations, interventions or demonstrations without being hindered by their nationality. Similarly, we hope to establish a system through which overseas doctors can learn new techniques alongside Japanese doctors, and to provide an environment where doctors from various countries can mingle with young doctors working at our hospital, as well as student physicians in participatory clinical training. We have been

actively accepting observership trainees per hospital ruling and advanced clinical trainees granted permission for hands-on clinical experience by the Ministry of Health, Labor and Welfare under the Exceptional Cases of the Medical Practitioners 'Act, Article 17, regarding Advanced Clinical Training of Foreign Medical Practitioners, etc.

Lastly, heightening the capability of physicians and medical staff to cater to international needs is an important factor in globalizing The University of Tokyo Hospital. To this end, the International Medical Center will attempt to cultivate personnel by hosting various international exchanges so as to further develop the hospital's capabilities to become an international hub in the field.

Center for Epidemiology and Preventive Medicine

Director & Associate Professor

Nobutake Yamamichi, M.D., Ph.D.

Deputy Director & Assistant Professor

Lumine Matsumoto, M.D., Ph.D.

Associates

Keiko Niimi, M.D., Ph.D., Yukari Masuda, M.D., Ph.D.

Hiroataka Matsuzaki, M.D., Ph.D., Eriko Hasumi, M.D., Ph.D., Chie Buijyo, M.D., Ph.D.,

Takako Nishikawa, M.D., Ph.D., Nobuyuki Sakuma, M.D., Ph.D.,

Homepage: <https://www.todai-yobouigaku-dock.jp/>
<https://www.h.u-tokyo.ac.jp/patient/depts/yobouigaku/>

Introduction and Organization

Following the inauguration of a new Central Clinical Service Building in November 2006 in the University of Tokyo Hospital, the Center for Epidemiology and Preventive Medicine was established on January 1st, 2007, within the Central Clinical Facilities and the relevant regulations were revised. On January 9th, the Working Group for the Establishment of the Center for Epidemiology and Preventive Medicine was organized; on April 1st, Steering Committee for the Establishment of the Center for Epidemiology and Preventive Medicine was organized; on June 4th, the department started offering its services on a trial basis (in-hospital services) and was officially inaugurated in July, starting to provide public services.

The principal objectives of the establishment of the Center for Epidemiology and Preventive Medicine are 1) to scientifically demonstrate the utility and effectiveness of examinations and preventive interventions, 2) to integrate a vast amount of clinical data and health-related information to develop more efficient models for disease management, 3) through 1) and 2), to promote preventive medicine and medicine for health promotion in an effort to contribute to the

improvement of public health, and 4) to train medical personnel who can put above-mentioned 1), 2) and 3) into practice.

In these twelve years since the official opening, our center has increased the number of examinees from ten subjects per day to twelve per day (March 2018). Following the reorganization in April 2018, the Center was transferred to the 15th floor of the inpatient building B in September 2018. As the area for examination was expanded, we have been able to increase the number of examinees to 16 in October 2018, 20 in April 2019, 22 in January 2021, and 25 in October 2022. Most of the examinations except for MRI and CT scan can be performed within our floor, which increased the convenience and comfort for the examinees.

In the administrative organization of the Center for Epidemiology and Preventive Medicine, the Director directly under the head of the hospital is responsible for the entire organization. Examinations in the Department are administered in collaboration with three Central Clinical Facilities (Clinical Laboratory Center, Radiological Center, and Department of Endoscopy and Endoscopic Surgery) and four Clinical

Divisions (Gastroenterology, Breast and Endocrine Surgery, Gynecologic Surgery and Ophthalmology and Vision Collection).

The staff of the Center for Epidemiology and Preventive Medicine is composed of nine physicians. Three of the regular physicians also perform upper gastrointestinal endoscopy and colonoscopy. Our department also has 11 nurses, six assistant clerks, and three medical clerk.

Clinical activities

In addition to basic examinations, we provide ten optional examinations: 1) comprehensive cardiovascular examinations, 2) comprehensive cerebrovascular examinations, 3) checkup for dementia, 4) colorectal cancer screening, 5) uterine cancer screening, 6) breast cancer screening, 7) lung cancer screening, 8) tumor marker diagnosis, 9) estimation of gastric cancer risk, and 10) pancreatic cancer screening. While meeting the needs of examinees, we have increased the number of the optional examinations.

The physicians of our department are responsible for analyzing the results of examinations and performing overall evaluations. We take plenty of time to perform comprehensive medical examinations and instantly write a referral letter to each department in the University of Tokyo Hospital when we find any abnormality through the examinations. Formally, the examinee is notified in writing within approximately three weeks after the examination. We also offer each examinee a free consultation so that we can help him/her understand the results or decide whether to have further detailed examination.

Teaching activities

We started clinical teaching for medical students in April 2017. Following the lecture of preventive medicine, students observe explanations by physicians to the examinees. They learn not only how to apply preventive medicine to practice, but also the manner of physicians to examinees.

Research activities

The University of Tokyo Hospital is expected not only to provide its service of comprehensive medical

examinations but also to promote evidence-based practice and scientific examinations, which is the mission of our department. Academically, we aim to establish a database from clinical data and to promote epidemiological research. This will enable us to prevent disease based on scientific data. We have conducted cross-sectional/longitudinal analysis. We also work in collaboration with other departments in our hospital and other facilities.

Past activities

The total number of examinees (who had basic examinations and optional examinations) in the FY 2023 was 10011 including 3491 in basic examinations, 596 in complete cardiovascular examinations, 748 in complete cerebrovascular examinations, 132 in check up for dementia, 481 in colorectal cancer screening, 742 in uterine cancer screening, 872 in breast cancer screening, 869 in lung cancer screening, 1383 in tumor marker diagnosis, 402 in estimation of gastric cancer risk, 295 in pancreatic cancer screening, and 6 in upper gastrointestinal endoscopy (later). Respiratory function test has been cancelled from March 31, 2020 due to coronavirus.

One of the important roles of our center is to provide the appropriate medicine to the examinees when any abnormal finding was detected. We provide referral letters to the department within/outside of our hospital for detailed examination or treatment, according to the request by the examinees. Prompt reference to the medical department in the University of Tokyo Hospital is one of the most contributable factors for the satisfaction of the examinees. In the FY 2023, we issued 1722 letters of referral to other departments in our hospital and 55 to other hospitals.

We have expanded our public relations efforts. We renewed brochures and 15,000 brochures were delivered during the FY 2021.

We have updated our original website (<https://www.todai-yobouigaku-dock.jp/>) and offer up-to-date information to the examinees. We also renewed brochure, distributing 15,000 copies within our hospital and on and off campus of the University of Tokyo as well. We have established preferential treatment system for graduates, faculty and staff to acquire new examinees.

The University of Tokyo Hospital established the Center for International Preventive Medicine in April 2020 and started to provide public services in July 2022. We offer full cooperation to the Center for International Preventive Medicine management.

References

Academic Papers in English

1. Takeuchi C, Sato J, Yamamichi N, Kageyama-Yahara N, Sasaki A, Akahane T, et al: Marked intestinal trans-differentiation by autoimmune gastritis along with ectopic pancreatic and pulmonary trans-differentiation. *J Gastroenterol*. Epub 2023 Nov 14.
2. Takeuchi T, Kubota T, Nakanishi Y, Tsugawa H, Suda W, Yamamichi N, et al: Gut microbial carbohydrate metabolism contributes to insulin resistance. *Nature* 2023, 621(7978):389-395.
3. Takahashi M, Shimamoto T, Ozeki A, Matsumoto L, Yamamichi N, et al: Relationship Between Sleep and Obesity: A Cross-sectional and Longitudinal Observational Study of Healthy Adults in Japan. *Ningen Dock International* 2023, 10(1):39-49.
4. Sakurai K, Nagai A, Ando T, Sakai Y, Ideta Y, Hayashi Y, Yamamichi N et al: Cytomorphology and Gene Expression Signatures of Anchorage-independent Aggregations of Oral Cancer Cells. *Cancer Genomics Proteomics* 2023, 20(1):64-74.
5. Nagao S, Takahashi Y, Denda T, Tanaka Y, Yamamichi N, et al: Reduced DEFA5 Expression and STAT3 Activation Underlie the Submucosal Invasion of Early Gastric Cancers. *Digestion* 2023:1-14.
6. Mizutani S, Takahashi Y, Shimamoto T, Yamamichi N, et al: Performing the ABC Method Twice for Gastric Cancer Risk Stratification: A Retrospective Study Based on Data from a Large-Scale Screening Facility. *Diagnostics (Basel)* 2023, 13(7).
7. Mizuno Y, Nakanishi K, Uemura K, Kaneko H, Daimon M, Yamamichi N, Komuro I: Association Between Arterial Stiffness and Bone Mineral Density in the Japanese General Population. *Ningen Dock International* 2023.
8. Fukagawa K, Takahashi Y, Yamamichi N, Kageyama-Yahara N, Sakaguchi Y, et al: Transcriptome analysis reveals the essential role of NK2 homeobox 1/thyroid transcription factor 1 (NKX2-1/TTF-1) in gastric adenocarcinoma of fundic-gland type. *Gastric Cancer* 2023, 26(1):44-54
9. Hasumi E, Fujiu K, Komuro I. Multiple recurrent episodes of pacemaker-associated postcardiac injury syndrome. *Heart Rhythm Case Rep*. 2023 Jan 25;9(4):244-247.
10. Nakanishi K, Daimon M, Fujiu K, Iwama K, Yoshida Y, Hirose K, Mukai Y, Yamamoto Y, Nakao T, Oshima T, Matsubara T, Shimizu Y, Oguri G, Kojima T, Hasumi E, Morita H, Komuro I. Prevalence of glucose metabolism disorders and its association with left atrial remodelling before and after catheter ablation in patients with atrial fibrillation. *Europace*.; 25(5): euad119. DOI: 10.1093/europace/euad119
11. Mukai Y, Nakanishi K, Daimon M, Iwama K, Yoshida Y, Hirose K, Yamamoto Y, Seki H, Nakao T, Oshima T, Matsubara T, Shimizu Y, Oguri G, Kojima T, Hasumi E, Fujiu K, Morita H, Komuro I. Prevalence, Associated Factors, and Echocardiographic Estimation of Left Atrial Hypertension in Patients With Atrial Fibrillation. *J Am Heart Assoc*. 2023 Sep 13:e030325. DOI: 10.1161/JAHA.123.030325
12. Oida M, Hasumi E (Corresponding author), Goto K, Kani K, O Tsukasa, Matsubara TJ, Shimizu Y, Oguri G, Kojima T, Fujiu K, Komuro I. The estimated glomerular filtration rate predicts pacemaker-induced cardiomyopathy. *Scientific Reports* 2023;13(1):16514. DOI: 10.1038/s41598-023-43953-7
13. Kazutoshi Hirose, Koki Nakanishi, Masao Daimon, Kentaro Iwama, Yuriko Yoshida, Yasuhiro Mukai, Yuko Yamamoto, Tomoko Nakao, Tsukasa Oshima, Takumi Matsubara, Ieei Komuro. Association of atrial fibrillation progression with left atrial functional reserve and its reversibility. *Journal of the American Heart Association* 13(1) e032215
14. Gaku Oguri, Katsuhito Fujiu, Tsukasa Oshima, Yu Shimizu, Eriko Hasumi, Toshiya Kojima, Issei Komuro. Cryoballoon ablation for paroxysmal atrial fibrillation mildly improves lung function: An observational study. *Medicine* 102(46) e35991

Medical Community Network and Discharge Planning Center

Associate Professor

Masahiko Sumitani, M.D., Ph.D. (concurrently)

Assistant Professor

※The following information is the same as that of the previous year for certain reasons.

Homepage <https://www.h.u-tokyo.ac.jp/english/centers-services/central-clinical-facilities/medical-community-network-and-discharge-planning/index.html>

Introduction and Organization

In April 1997, plans for the Department of Medical Social Service and Welfare were initiated by the University of Tokyo Hospital with the aim of supporting inpatients upon discharge. The Department was officially authorized in April 2000, the first among national universities. In April 2005, the Department began providing assistance to outpatients referred from other hospitals and was renamed the Department of Medical Community Network and Discharge Planning. Further, in 2019, the department changed the name to Medical Community Network and Discharge Planning Center. The Center provides assistance to outpatients referred from local medical institutions, to inpatients being discharged to their homes, and to inpatients being transferred to local medical institutions.

Clinical activities

Assistance to patients receiving medical treatment: The Department provides assistance to outpatients referred from local medical institutions. Our staff helps patients make appointments and follow procedures to receive medical treatment. The Department assists new outpatients in arranging general consultations, helps outpatients schedule specialized treatment, and provides assistance to patients who have been referred to a specific physician.

Assistance to inpatients upon discharge: The Department provides assistance to patients for whom transfer to a local medical institution or discharge to home if need arises.

Many of such patients are highly dependent on medical care due to the severity of their condition. For those receiving medical care at home, our department staff arranges home visits by primary care doctors and nurses. For patients being transferred to local institutions, our staff provides assistance both to general hospitals and hospice care units.

Home Care Support (Home Care Support clinic): Our Home Care Support Clinic, which offers home care support to our outpatients, has been running since January 2003. The clinic supports the implementation and coordination of home care services, and refers outpatients requesting hospital admission to other hospitals or facilities.

Consultation by Social Worker (Consultation on Recuperation): Our consultation service provided by social workers has been running since 2012. Our social workers mainly consult enquiries regarding patient recuperation.

Transferring out patients to local institutes: Aiming to defining the distinction of the medical role between the University Hospital and local institutes and facilitate transferring our outpatients to them, the proportion of such transferring patients to first-visit patients keeps more than 80%.

Teaching activities

We educate undergraduate students of the Medical Social Working and Welfare of other university.

Research activities

Our research field covers investigating appropriate patient numbers for assistance to inpatients upon discharge in the University hospital; and investigating how to assist working and job in patients with severe illness.

Cancer Resource Center

Chief

Sachiyo Nomura, M.D., Ph.D.

Associate chief

Mayuyo Mori, M.D., Ph.D.

Counseling staff

Kunie Wakao, RN., Yuko Irisawa, RN., Takako Wakeda, M.D., Ph.D.

※The following information is the same as that of the previous year for certain reasons.

Homepage <http://www.h.u-tokyo.ac.jp/patient/depts/gansoudan/>

Introduction and Organization

As part of national efforts to address cancer, the government has been establishing a network of “cancer care hub hospitals.” In response to its being designated as a regional cancer care hub hospital in 2008, the University of Tokyo Hospital established the Cancer Patient Support Center to provide consultations to cancer patients and their families as well as residents in neighboring communities with the aim of leading them to appropriate departments and facilities.

Medical Services

Provision of information if patient contracts cancer

If a person gets cancer, the first thing they need to do is collect information on cancer. The Cancer Counseling and Support Center provides information and booklets on different types of cancer.

Furthermore, the person needs to accurately understand the doctors’ explanations to select the best treatment for oneself from the various options presented by doctors. At the Cancer Counseling and Support Center, we explain difficult medical terms in simple language, and we help patients understand their doctors’ advice.

Various kinds of advice related to the medical care of cancer

If a person contracts cancer, besides the medical problem of what kind of treatment to undergo and where, there are also issues related to medical care when receiving treatment, such as medical expenses, how to get along after being discharged from hospital, job, and nursing services. The Cancer Counseling and Support Center provides patients with advice and support so that they can resolve such social worries.

Provision of information on second opinions

The Center provides information on how to get a second opinion and on facilities that provide second opinions.

Various kinds of advice related to the appearance changes caused by cancer treatment

Cancer treatment often causes appearance changes such as hair loss and skin pigmentation. The center provides patients with practical advice and support about wig and cover make-up.

Provision of general information and advice on cancer

The Center sends out and provides information to people who do not have cancer but who want to find

out about cancer, for instance the treatment and screening for it.

Open hours

If you have any queries, please contact us on 03-5800-9061 between 9am-12noon, 1pm-4pm weekdays.

Research activities

Our research field covers the relation between appearance changes caused by cancer therapy and Patients' quality of life.

Clinical Research Promotion Center

Professor, Director

Takashi Moritoyo, M.D., Ph.D.

Associate Professor, Vice Director

Tatsuya Maruyama, M.D., Ph.D.

Project Associate Professor,

Ruri Kaneda, M.D., Ph.D.

Project Lecturer

Kosuke Kashiwabara, Ph.D.

Assistant Professor

Takuya Kawahara, Ph.D., Mihoko Shibuya, M.D., Ph.D., Mariko Inoue, M.D., Ph.D.

Project Assistant Professor

Miki Ohta, M.D., Ph.D., Ryo Matsuoka, M.D., Ph.D., Yosuke Inaba, Ph.D. (from August)

Homepage <https://www.h.u-tokyo.ac.jp/english/centers-services/clinical-research-division/clinical-research-promotion-center/index.html>

History and Organization

The Clinical Research Promotion Center was established in 2019. It originated from Clinical Trial Managing Center, which was established in 1998, and subsequently the former Clinical Research Center, which was established in 2001. Currently, it belongs to the Clinical Research Services of the hospital and provides supports not only for clinical trials but also for investigator-initiated (independent) clinical studies.

However, given the increasing diversity and volume of clinical research conducted in the University of Tokyo Hospital, demand mounted for the structural framework to provide support for multi-center collaborative studies, research on new technology in evidence-based medicine and translational research etc. In response to such diversified demands, the former Clinical Research Center was reorganized in April 2010 into the Clinical Research Support Center, enabling

strengthened support and expeditious promotion of clinical research.

The Center at the beginning consisted of Site Coordinating Unit, roughly equivalent to the former Clinical Research Center, and Central Coordinating Unit, which provides coordinating functions for research such as multicenter trials.

Site Coordinating Unit is comprised of the [Institutional Review Board (IRB) Secretariat Division] [Investigational Drug/Information Control Division] and [Clinical Research Coordinator Division], each charged with IRB secretarial affairs, management of drugs used in the conduct of clinical research and provide assistance with safety information reporting, and clinical research coordination activities. In addition to the existing Consultation Division, new divisions such as Operation Division, Biostatistics Division, Data Management Division, Monitoring Division and Safety Information Division and

Operation Division have been added to the Central Coordinating Unit.

In 2011, the Center was selected as an Ministry of Health, Labour and Welfare (MHLW)-funded Center of Excellence for early stage and exploratory clinical trials of drugs for psychiatric and neurological diseases, enabling the Center to reinforce the staff and to be equipped with Phase 1 Unit that can conduct Phase I first-in-human clinical trial. Thus, the third unit, i.e., P1 Unit was established in May 2012 with 13 beds exclusively used for clinical studies, making it possible to provide seamless support to the complete clinical development process.

We revised rules and procedures in compliance with the “Ethical Guidelines for Medical and Health Research Involving Human Subjects” that came into effect in April 2015 and examined the realignment of functions related to clinical research aimed at strengthening governance functions of the University of Tokyo Hospital. In January 2015, we established Clinical Research Governance Division and later Office of Clinical Quality Assurance & Compliance was created independently of the Clinical Research Support Center responsible for conducting quality assurance audits. Also, with the aim of improving the quality of clinical research in clinical departments, we appointed 1-2 to staff from each clinical department to serve as concurrent clinical instructors, thereby strengthening the supervision and monitoring system in the departments.

In April 2016, ethical review process of specific clinical trials (involving invasion and intervention) was transferred to the Faculty of Medicine to ensure transparency of clinical research. IRB for reviewing industry-initiated and investigator-initiated clinical trials was newly established in the hospital. With respect to the IRB’s secretarial and administrative duties, the Center will continue to take responsibilities. Moreover, an Specific Clinical Research Steering Committee was established under the hospital director and external audit committee to seek external evaluation. In addition, we integrated clinical research management system by strengthening management of conflicts of interest, created educational environment for clinical research personnel, formed collaboration with the Clinical Evaluation and Safety Division to strengthen safety management system. As a result, the

University of Tokyo Hospital received accreditation as a clinical research core hospital under Medical Care Act in March 2016.

Based on the enforcement of the Act on ensuring the Safety of Regenerative Medicine, the Certified Special Committee for Regenerative Medicine was established at the Central Administrative Office of the university, and Clinical Research Support Center undertook responsibilities for secretarial and administrative affairs.

Furthermore, in order to clarify that it is an organization that promotes clinical research, the Center was renamed as Clinical Research Promotion Center in December 2019. The Center was reorganized into 8 departments.

<Investigator-Initiated Clinical Trials Promotion Department>

The department is responsible for: (1) secretariat duties for investigator-initiated clinical trials, advanced medical treatment, patient-proposed healthcare services and regenerative medicine; (2) Providing advice and support regarding development strategy, trial design, pharmaceutical affairs, funding, intellectual property, industry-academia collaboration, etc.; (3) Providing support (study management, monitoring, safety information support, data management, biostatistics, etc.) to promote investigator-initiated trials.

<Industry-Initiated Clinical Trials Promotion Department>

The department is responsible for: (1) Supporting the safe and smooth implementation of industry-initiated clinical trials; (2) CRC operations, study drug management, and clinical psychological examinations.

<IRB Office>

The office is responsible for: (1) Managing the Institutional Review Board (IRB) and coordinating with related departments; (2) Providing support for investigators who wish to be reviewed by the IRB.

<Dedicated Clinical Trial Ward Department (P1 Unit)>

The department is responsible for: (1) The safe and smooth conduct of clinical trials related to pharmaceuticals and medical devices; (2) the recruitment of human subjects.

<Medical Safety Management Department>

The department is responsible for Management of

safety reports and collection and reporting of safety information. (In March 2023, the Personal Information Management Office was abolished and its name was changed to the Medical Safety Management Department.)

<Planning, Strategy and Management Department>

The department is responsible for: (1) Planning for responding to authorities, acquisition of funds for projects and expansion of the Center's functions; (2) Management of the Center's budget, personnel and documents; (3) General management of the Center's information system, including information security; (4) Education and training for and provision of information to investigators who wish to conduct clinical research; (5) Management, education and training of clinical research trainers; (6) Management of the progress of clinical research conducted at the University of Tokyo Hospital.

<Network Promotion Department>

The department is responsible for: (1) Secretariat duties for the National University Hospital Clinical Research Promotion Initiative joined by 44 hospitals of 42 national universities; (2) Secretariat duties for the University of Tokyo Hospital related to the University Hospital Clinical Trial Alliance which is a regional network of national university hospitals involved in clinical research (consisting of 8 universities and 9 hospitals in the Kanto-Koshinetsu region).

<Clinical Trials Patient Counseling Department>

The department is responsible for providing consultation services for patients and citizens who would like to use advanced medical care and public relation activities.

Clinical Research Promotion Activities

The Clinical Research Promotion Center provides wide range of support from pre-application consultation, secretariat for the IRB to supporting the implementation and reporting of clinical trials. In 2002, during the time of the Clinical Trials Department, the Center began providing assistance for investigator-initiated clinical trials evaluating therapeutic drugs and studies involving unapproved drugs in addition to conventional clinical trials (from 2015 use of unapproved drugs in clinical research was transferred

to Research Ethics Committee of Graduate School of Medicine and School of Medicine, and from 2018, it was moved to Evaluation Committee on Unapproved News Drugs). From 2009, we have been providing support for all invasive and interventional clinical research.

For industry-initiated clinical trials, we hold a preliminary hearing session (called "protocol presentation") in order to shorten the period from application to approval and enhance the content of review. As a result, we could avoid re-review by the IRB due to lack of information.

Since 2002, Clinical research coordinators (CRC) of the Center have been supporting all clinical trials for approval and post marketing trials. We started to support in part investigator-initiated research from 2004. We started providing CRC support to investigator-initiated research on a beneficiary-pays basis from 2005 and clinical pharmacology studies in healthy volunteers from 2012. CRCs exclusively involved in investigator-initiated research, have been employed as needed. CRC support for Advanced Medical Care Program B which University of Tokyo Hospital participated as a head investigational site was initiated in 2017.

As part of patient awareness activities, we continued updating the patient homepage, prepared leaflets and distributed them at outpatient reception counters. The leaflets contain information about research currently recruiting participants. In addition, Clinical Trial Patient Consulting Room provides consultation to patients or their families participating in clinical trials or who are considering to enroll in a clinical trial in close cooperation with the Patients Relations and Clinical Ethics Center, Cancer Consulting and Support Center, Department of Medical Community Network and Office of Medical Accounting.

In order to support the promotion of investigator-initiated clinical trials conducted by physicians etc. the Center has been implementing the system successively partly supported by the MHLW-funded Early-Stage and Exploratory Clinical Trial Project that started in 2011. In order to comply with the "Ethical Guidelines for Medical and Health Research Involving Human Subjects enacted in 2014", we classified clinical research according to guidelines, validation studies and exploratory studies and started accepting all assistance

requests for validation studies, starting from May 2015. Regarding the exploratory studies, monitoring and data management were to be carried out by each clinical department, the Center undertook responsibility for supervision of the quality control (QC). The Center manages SAE (severe adverse event) reporting and supports various safety reporting in order to ensure that clinical studies are conducted safely.

Since its establishment in May 2012, the Phase 1 Unit (P1 Unit) has undertaken various preparations to respond to early phase clinical research, such as development of SOP program, procedure manuals, establishment of in-house collaboration system, on-the-job training for staff and the system for recruiting health volunteers. P1 Unit conducted its very first clinical study in October 2012. In September 2018 the unit was relocated as a new ward with augmented 21 beds exclusively aimed for clinical trial on the 12th floor of the Inpatient Building B, which was newly constructed in January 2018.

<University Hospital Clinical Trial Alliance>

University Hospital Clinical Trial Alliance (UHCT Alliance) comprised of 6 national university hospitals (The University of Tokyo, Niigata University, Gunma University, Tsukuba University, Tokyo Medical and Dental University and Chiba University) located in the central part of Japan was established in February 2006. In February 2007 Shinshu University and in February 2013 Yamanashi University joined the Alliance as the 7th and 8th member university, respectively. And in February 2015, the Institute of Medical Science the University of Tokyo joined the Alliance as the 8th member university 9 hospitals.

As part of the Alliance activities the University of Tokyo developed a clinical research support system UHCT ACRess jointly with Fujitsu and started operation in 2011, to support clinical researchers in the quality and project management. In addition, we developed curriculum called CREDITS (*Continuous Systematic Education & Training Curriculum for Clinical Researchers and Specialists*) jointly with the Education and Training Division in 2015. Currently, we are expanding the use outside the alliance members.

<National University Hospital Clinical Research Initiative>

In October 2012, the University of Tokyo took the lead in establishing the National University Hospital

Clinical Research Initiative (NUH-CRI). The administrative affairs of the Initiative has been supported by the secretariat located within the University of Tokyo Hospital since the preparatory meeting in July 2012. The initiative considered sharing education curriculum as one of the common educational programs of national university hospitals nationwide. Feasibility assessment system was developed for investigator-initiated clinical study to support the promotion of clinical trials conducted at the National University Hospitals.

Education/Training

The Center has been accepting M3/M4 students for training course in 'Clinical Clerkship' since it become mandatory in 2013. From 2017, we have been offering systematic lectures on "Clinical Research" for M2 medical students. In addition, we have been accepting junior resident physicians for training as a part of the M.D. residency-training program.

Since 2015, it has been providing education and training for students and researchers. In particular, we have developed curriculum called CREDITS (*Continuous Systematic Education & Training Curriculum for Clinical Researchers and Specialists*) jointly with UHCT Alliance.

Clinical instructor system was established in 2015, in which physicians recommended by each clinical department hold an additional position at the Clinical Research Promotion Center concurrently with their department, centrally manage information on clinical research conducted in their own departments and hold regular training sessions to disseminate information on education and training programs.

The University of Tokyo Hospital has conducted annual CRC training program for national, public and private university hospitals since 2010, commissioned by the Ministry of Education, Culture, Sports, Science and Technology. As a part of the Japan Agency for Medical Research and Development (AMED) project, training workshop for clinical research personnel has been held since 2017, sponsored by the University of Tokyo.

Furthermore, in response to the shortage of biostatisticians, biostatistics and bioinformatics course was established by AMED, at the university hospital.

In 2018, master's course was also established within the Graduate School of Interdisciplinary Information Studies and the Clinical Research Promotion Center has established a system to conduct practical training for course participants.

Research Activities

In April 2007, with the cooperation of the Biostatistics Department, the Center launched the Clinical Trial Data Management course (endowed course).

As of fiscal 2023, the Center was involved in scientific meetings, which include The Japan Society of Clinical Pharmacology and Therapeutics, Japan Society of Clinical Trials and Research, etc. As for publications such as academic papers, 36 papers were produced (35 papers in English and 1 papers in Japanese).

Publications

- 1) Nozuma S, Matsuura E, Tashiro Y, Nagata R, Ando M, Hiramatsu Y, Higuchi Y, Sakiyama Y, Hashiguchi A, Michizono K, Higashi K, Matsuzaki T, Kodama D, Tanaka M, Yamano Y, [Moritoyo T](#), Kubota R, Takashima H. Efficacy of l-Arginine treatment in patients with HTLV-1-associated neurological disease. *Ann Clin Transl Neurol*. 10:237-245, 2023
- 2) [Moritoyo T](#), Nishimura N, Hasegawa K, Ishii S, Kirihara K, Takata M, Svensson AK, Umeda-Kameyama Y, [Kawarasaki S](#), Ihara R, [Sakanaka C](#), [Wakabayashi Y](#), Niizuma K, Tominaga T, [Yamazaki T](#), Hasumi K. A first-in-human study of the anti- inflammatory profibrinolytic TMS-007, an SMTP family triprenyl phenol. *Br J Clin Pharmacol*. 89:1809-1819, 2023
- 3) Ikeda M, Okugawa S, [Kashiwabara K](#), [Moritoyo T](#), Kanno Y, Jubishi D, Hashimoto H, Okamoto K, Tsushima K, Uchida Y, Mitsumura T, Igari H, Tsutsumi T, Araoka H, Yatera K, Yamamoto Y, Nakamura Y, Otani A, Yamashita M, Wakimoto Y, Shinohara T, Adachi-Katayama M, Oyabu T, Kanematsu A, Harada S, Takeshita Y, Nakano Y, Miyazaki Y, Sakao S, Saito M, Ogura S, Yamasaki K, Kawasuji H, Hataji O, Inoue J, Seto Y, Moriya K. Multicenter, single-blind, randomized controlled study of the efficacy and safety of favipiravir and nafamostat mesilate in patients with COVID-19 pneumonia. *Int J Infect Dis*. 128:355-363, 2023
- 4) Mitsui J, Matsukawa T, Uemura Y, [Kawahara T](#), Chikada A, Porto KJL, Naruse H, Tanaka M, Ishiura H, Toda T, [Kuzuyama H](#), [Hirano M](#), [Wada I](#), [Ga T](#), [Moritoyo T](#), Takahashi Y, Mizusawa H, Ishikawa K, Yokota T, Kuwabara S, Sawamoto N, Takahashi R, Abe K, Ishihara T, Onodera O, Matsuse D, Yamasaki R, Kira JI, Katsuno M, Hanajima R, Ogata K, Takashima H, Matsushima M, Yabe I, Sasaki H, Tsuji S. High-dose ubiquinol supplementation in multiple-system atrophy: a multicentre, randomised, double-blinded, placebo-controlled phase 2 trial. *E Clinical Medicine*. 59:101920, 2023
- 5) Okugawa S, Ikeda M, [Kashiwabara K](#), [Moritoyo T](#), Kohsaka T, Shimizu T, Hagiya H, Hasegawa K, Otsuka F, Miwa A, Kisimoto N, Mizoguchi A, Imamura A, Ikeuchi K, Tsutsumi T, Jubishi D, Hashimoto H, Okamoto K, Harada S, Inoue JI, Seto Y, Moriya K. Antiviral effect and safety of nafamostat mesilate in patients with mild early-onset COVID-19. An exploratory multicenter randomized controlled clinical trial. *Int J Antimicrob. Agents*. 62:106922, 2023
- 6) [Ohta M](#), Miyawaki S, Yokota S, Yoshimoto M, Maruyama T, Koide D, [Moritoyo T](#), Saito N. Causality Assessment Between Drugs and Fatal Cerebral Haemorrhage Using Electronic Medical Records: Comparative Evaluation of Disease-Specific and Conventional Methods. *Drugs Real World Outcomes*. 11:221-229, 2024
- 7) Niizuma K, Nishimura N, Hasegawa K, [Moritoyo T](#), Kudo K, Bell J, Wald M, Umeda Y, Kuribayashi K, Toda Y, Tominaga T, Hasumi K. Anti-Inflammatory Thrombolytic JX10 (TMS-007) in Late Presentation of Acute Ischemic Stroke. *Stroke*. 55:2786-2794, 2024
- 8) Yamakawa N, Tago F, Nakai K, Kitahara Y, Ikari S, Hojo S, Hall N, Aluri J, Hussein Z, Gevorkyan H, [Maruyama T](#), Ishizaka S, Yagi T. First-in-Human Study of the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of E6742, a Dual Antagonist of Toll-like Receptors 7 and 8, in Healthy Volunteers. *Clin Pharmacol Drug Dev*. 12:363-375, 2023

- 9) Qin Q, Oe M, Nakagami G, Kashiwabara K, Sugama J, Sanada H, Jais S. The effectiveness of a thermography-driven preventive foot care protocol on the recurrence of diabetic foot ulcers in low-medical resource settings. An open-labeled randomized controlled trial. *International Journal of Nursing Studies*. 146:104571, 2023
- 10) Mayanagi S, Oba K, Aoyama T, Tanaka K, Kanda M, Honda M, Maeda H, Kashiwabara K, Muto M, Sakamoto J, Yamagishi H, Yoshikawa T. Feasibility and safety of adjuvant chemotherapy for resected colorectal cancer in patients with renal insufficiency. A pooled analysis of individual patient data from five Japanese large-scale clinical trials. *Anticancer Research*. 43: 3089-3095, 2023
- 11) Mitsutake Y, Ishii J, Fukumoto Y, Ito S, Kashiwabara K, Uemura K, Matsuyama Y, Sugiyama Y, Ozaki Y, Iimuro S, Iwata H, Sakuma I, Nakagawa Y, Hibi K, Hiro T, Hokimoto S, Miyauchi K, Daida H, Shimokawa H, Saito Y, Kimura T, Matsuzaki M, Nagai R. Differential prediction of high-sensitivity cardiac troponin-I, but not N-terminal pro-brain natriuretic peptide, in different pitavastatin doses on cardiovascular events in stable coronary artery disease. *International Journal of Cardiology*. 387:131138, 2023
- 12) Shinya Y, Hasegawa H, Shin M, Kashiwabara K, Kawashima M, Hanakita S, Koga T, Koizumi S, Katano A, Suzuki Y, Saito N. Age-dependent hemorrhage risk and obliteration benefit after radiosurgery for brain arteriovenous malformation. *International Journal of Radiation Oncology, Biology, Physics*. 116:1126-1134, 2023
- 13) Morinaga J, Kashiwabara K, Torigoe D, Okadome Y, Aizawa K, Uemura K, Kurashima A, Matsunaga E, Fukami H, Horiguchi H, Sato M, Sugizaki T, Miyata K, Kadomatsu T, Mukoyama M, Miyauchi K, Hokimoto S, Fukumoto Y, Hiro T, Hibi K, Nakagawa Y, Sakuma I, Ozaki Y, Iwata H, Iimuro S, Daida H, Shimokawa H, Kimura T, Matsuzaki M, Saito Y, Matsuyama Y, Nagai R, Oike Y. Plasma ANGPTL8 levels and risk for secondary cardiovascular events in Japanese patients with stable coronary artery disease receiving statin therapy. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 43:1549-1559, 2023
- 14) Hasegawa H, Shin M, Shinya Y, Kashiwabara K, Kikuta S, Kondo K, Saito N. Long-term outcomes of non-vascularized multilayer fascial closure technique for dural repair in endoscopic transnasal surgery. The efficacy, durability, and limitations. *World Neurosurg*. 175:e97-107, 2023
- 15) Mitake S, Wada-Hiraike O, Kashiwabara K, Nakamura A, Nasu R, Hine M, Matsuyama Y, Fujii T, Osuga Y. Distribution of the follicular and luteal phase lengths and their age-dependent changes in Japanese women. A large population study. *Reproductive Medicine and Biology*. 22:e12516, 2023
- 16) Aoyama T, Oba K, Honda M, Muto M, Mayanagi S, Maeda H, Kanda M, Kashiwabara K, Sakamoto J, Yoshikawa T. The clinical impacts of postoperative complications after colon cancer surgery for the clinical course of adjuvant treatment and survival. *International Journal of Clinical Oncology*. 28:777-784, 2023
- 17) Murayama R, Abe-Doi M, Masamoto Y, Kashiwabara K, Komiyama C, Sanada H, Kurokawa M. Verification study on the catheterization of an upper arm vein using the new long peripheral intravenous catheter to reduce catheter failure incidence. A randomized controlled trial. *Drug Discoveries & Therapeutics* 17:52-59, 2023
- 18) Nakagawa-Nagahama Y, Igarashi M, Miura M, Kashiwabara K, Yaku K, Fukamizu Y, Sato T, Sakurai T, Nakagawa T, Kadowaki T, Yamauchi T. Blood levels of nicotinic acid negatively correlate with hearing ability in healthy older men. *BMC Geriatrics*. 23:97, 2023
- 19) Kage H, Shinozaki-Ushiku A, Ishigaki K, Sato Y, Tanabe M, Tanaka S, Tanikawa M, Watanabe K, Kato S, Akagi K, Uchino K, Mitani K, Takahashi S, Miura Y, Ikeda S, Kojima Y, Watanabe K, Mochizuki H, Yamaguchi H, Kawazoe Y, Kashiwabara K, Kohsaka S, Tatsuno K, Ushiku T, Ohe K, Yatomi Y, Seto Y, Aburatani H, Mano H, Miyagawa K, Oda K. Clinical utility of Todai OncoPanel in the setting of approved comprehensive cancer genomic profiling tests in Japan. *Cancer Science* 114:1710-1717, 2023

- 20) Suzuki A, Yamaguchi R, Kim L, Kawahara T, Ishii-Takahashi A. Effectiveness of mock scanners and preparation programs for successful magnetic resonance imaging: a systematic review and meta-analysis. *Pediatr Radiol*. 53:142-158, 2023
- 21) Uchida T, Kin T, Sato K, Koike T, Kiyofuji S, Takeda Y, Niwa R, Saito T, Takashima I, Kawahara T, Miyawaki S, Oyama H, Saito N. Reproducibility of Facial Information in Three-Dimensional Reconstructed Head Images: An Exploratory Study. *Curr Med Imaging*. 19:1387-1393, 2023
- 22) Fujimoto C, Kawahara T, Kinoshita M, Kamogashira T, Oka M, Ichijo K, Koda K, Yamasoba T, Iwasaki S. Inter-day and intra-day variations in effective intensity of noisy galvanic vestibular stimulation to improve postural stability in bilateral vestibulopathy. *J Vestib Res*. 33:423-429, 2023
- 23) Kiriya H, Kiyosue A, Minatsuki S, Kawahara T, Katsushika S, Kamon T, Hirose K, Shinohara H, Miura M, Saito A, Kikuchi H, Koda S, Hatano M, Ando J, Myojo M, Itoh N, Yamamoto K, Ikenouchi H, Takeda N, Komuro I. Potential value of saline-induced Pd/Pa ratio in patients with coronary artery stenosis. *Front Cardiovasc Med*. 9:1001833, 2023
- 24) Izumi S, Hagiwara Y, Matsuyama Y, Shiroya T, Taira N, Kawahara T, Konomura K, Noto S, Fukuda T, Shimozuma K. Impacts of the preceding cancer-specific health-related quality of life instruments on the responses to the subsequent EQ-5D-5L. *Health Qual Life Outcomes*. 21:3, 2023
- 25) Hagiwara Y, Shiroya T, Taira N, Kawahara T, Konomura K, Noto S, Fukuda T, Shimozuma K. Gradient Boosted Tree Approaches for Mapping European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Onto 5-Level Version of EQ-5D Index for Patients With Cancer. *Value Health*. 26:269-279, 2023
- 26) Oka M, Ichijo K, Koda K, Kamogashira T, Kinoshita M, Igarashi K, Kawahara T, Takashima I, Yamasoba T, Fujimoto C. Preceding Balance Disorders Affect Vestibular Function in Persistent Postural-Perceptual Dizziness. *J Clin Med*. 12:2589, 2023
- 27) Fuyama K, Ogawa M, Mizusawa J, Kanemitsu Y, Fujita S, Kawahara T, Sakamaki K, Oba K. Impact of correlations between prioritized outcomes on the net benefit and its estimate by generalized pairwise comparisons. *Stat Med*. 42:1606-1624, 2023
- 28) Tsutsumi Y, Tsuchiya A, Kawahara T. Publication hyper-inflation in the field of intensive care. *Intensive Care Med*. 49:706-707, 2023
- 29) Yamaguchi R, Kawahara T, Kotani T, Yazawa R, Suzuki A, Kano Y, Ishii-Takahashi A. The effectiveness of exercise programs accessible from home on children's and adolescents' emotional well-being: Systematic review & meta-analysis. *PCN Rep*. 2:e103, 2023
- 30) Ishii-Takahashi A, Kawakubo Y, Hamada J, Nakajima N, Kawahara T, Hirose A, Yamaguchi R, Kuwabara H, Okada T, Kano Y. Changes in child behavioral problems and maternal attachment towards children with attention-deficit/hyperactivity disorder following behavioral parent training: A pilot study. *Psychiatry Clin Neurosci*. 77:412-413, 2023
- 31) Fujimoto C, Oka M, Ichijo K, Kinoshita M, Kamogashira T, Sugawara K, Kawahara T, Yamasoba T. The effect of self-management vestibular rehabilitation on persistent postural-perceptual dizziness. *Laryngoscope Investig Otolaryngol*. 8:1014-1020, 2023
- 32) Hashimoto K, Kawahara T, Miyoshi K, Sato T, Itoh S. A case of carotid-axillary bypass for subclavian steal syndrome in an 83-year-old female undergoing hemodialysis. *Int J Surg Case Rep*. 112:108974, 2023
- 33) Nakayama A, Ishii N, Mantani M, Samukawa K, Tsuneta R, Marukawa M, Ohno K, Yoshida A, Hasegawa E, Sakamoto J, Hori K, Takahashi S, Komuro K, Hiruma T, Abe R, Norimatsu T, Shimbo M, Tajima M, Nagasaki M, Kawahara T, Nanasato M, Ikemage T, Isobe M. Remote Cardiac Rehabilitation With Wearable Devices. *Korean Circ J*. 53:727-743, 2023
- 34) Sato Y, Yamashita H, Kobayashi Y, Nagaoka K, Hisayoshi T, Kawahara T, Kuroda A, Saito N, Iwata R, Okumura Y, Yagi K, Aiko S, Nomura S, Kakimi K, Seto Y. Alterations in Intratumoral

Immune Response before and during Early-On Nivolumab Treatment for Unresectable Advanced or Recurrent Gastric Cancer. *Int J Mol Sci.* 24:16602, 2023

- 35) Inoue M, Nagafuchi Y, Ota M, Tsuchiya H, Tateishi S, Kanda H, Fujio K. Carriers of HLA-DRB1*04:05 have a better clinical response to abatacept in rheumatoid arthritis. *Sci Rep.* 13:15250, 2023

Division of Tissue Engineering

Director & Professor

Kazuto Hoshi, M.D., Ph.D.

Vice Director

Atsuhiko Hikita, M.D., Ph.D.

Project Professor

Makoto Komura, M.D., Ph.D., Atsuhiko Hikita, M.D., Ph.D.

Project Associate Professors

Kazumichi Yonenaga, D.D.S., M.D., Ph.D., Yasunori Omata, M.D. Ph.D.

Project Lecturer

Yukiyo Asawa, D.V.M., Ph.D. , Ono Sachiko, D.D.S., Ph.D., Asuka Terashima, Ph.D.

Project Associate Professor

Naoki Tsuji, D.D.S., Ph.D.

Research Associates

Itai Shunsuke, D.D.S., Ph.D.

Homepage <https://www.h.u-tokyo.ac.jp/patient/depts/te/>

Introduction and Organization

Division of Tissue Engineering was established as a special medical office in The University of Tokyo Hospital, in October 2001 and has a fully equipped 800 m² laboratory on the 8th floor of the In-patient Ward B. In May 2016, it moved to Molecular and Life Innovation building. Division of Tissue Engineering consists of Department of Bone & Cartilage Regenerative Medicine, Department of Tissue Stem cell/Life Dentistry, Department of Eat-loss Medicine, and Department of Clinical Stem Cell Biology. Researchers assigned to each department are conducting research with many graduate students. The researchers continue their studies to make the center function as a translational research center.

Tie-up with companies, technical transfer, patenting developed technologies, producing materials for treatment at a GMP level, safety evaluation studies and organization for clinical trials are necessary in order to

realize regenerative medicine, which is now recognized as a national project. As foundation and operation of venture companies as well as industry-university-government cooperation is essential to the success, it seems that state-level efforts are necessary. It is expected that broad progress in tissue engineering technologies and regenerative medicine contributes to treatment and drug discovery of all medical fields regardless of specialties.

October, 2001 Division of Tissue Engineering founded as a special medical office in the University of Tokyo Hospital.

June, 2002 Department of Corneal Tissue Engineering founded by a donation from HOYA health care CO., Ltd.

July, 2002 Department of Vascular Regeneration founded by a donation from Daiichi Pharmaceutical Co., Ltd.

July, 2002 Department of Bone & Cartilage Regenerative Medicine founded by a donation from

TAKEDA Chemical Industries., Ltd.

September, 2002 Department of Regeneration Medicine for Hematopoiesis founded by a donation from KIRIN Brewery Co., Ltd.

November, 2002 Department of Clinical Renal Regeneration founded by a donation from MOCHIDA Pharmaceutical Co., Ltd.

November, 2002 Department of MENICON Cartilage & Bone Regeneration founded by a donation from MENICON Co., Ltd.

March, 2003 The Cell Processing Center set up on the 8th floor of the In-patient Ward B.

June, 2005 Department of Corneal Tissue Regeneration was renewed by a donation from AMNIO TEC Co., Ltd.

July, 2005 Department of Bone & Cartilage Regenerative Medicine was renewed by a donation from TAKEDA Chemical Industries Co., Ltd.

September, 2005 Department of Regeneration Medicine for Hematopoiesis was renewed by a donation from KIRIN Brewery Co., Ltd.

November, 2005 Department of Clinical Renal Regeneration was renewed by a donation from MOCHIDA Pharmaceutical Co., Ltd.

November, 2005 By a donation from FUJISOFT ABC Co., Ltd. Department of MENICON Cartilage & Bone Regeneration was renewed to Department of Fuji Software ABC Cartilage & Bone Regeneration.

January, 2007 Laboratory for Pediatric Regenerative Medicine was founded by department of pediatric surgery.

July, 2007 Department of Bone & Cartilage Regenerative Medicine was renewed by a donation from Eli Lilly Japan K.K.

March, 2012 Department of Advanced Nephrology and Regenerative Medicine founded by a donation from Zenjinkai.

April, 2016 The Cell Processing & Banking Center set up on the 4th floor of the Molecular & Life Innovation Building.

November 2017 Change of the department name: Department of Cartilage & Bone Regeneration became Department of Cell & Tissue Engineering.

July, 2018 Department of Bone & Cartilage Regenerative Medicine was renewed by a donation from Avenue Cell Clinic, Kaneka Corporation, Rohto Pharmaceutical Co., Ltd. and Nichirei Corporation.

November, 2019 Department of Tissue Stem cell/Life Dentistry established by Dental assist Co., Ltd, Fuke hospital, Sashiogi Hospital, Ikegami Home Clinic and Inotec Co., Ltd.

April, 2020 Department of Eat-loss Medicine was founded by a donation from ITOEN Ltd.

October, 2020 Department of Cell & Tissue Engineering was terminated.

July, 2021 Department of Bone & Cartilage Regenerative Medicine was renewed by a donation from CPC Corporation, Kyowa Co., Ltd., Kanto Chemical Co., Inc. and Nichirei Corporation.

July, 2023 Department of Clinical Stem Cell Biology was founded by founded by a donation from Kohjin Bio Co., Ltd.

November, 2022 Department of Tissue Stem cell/Life Dentistry was renewed by SheepMedical Co.,Ltd.

Research activities

As for the Department of Bone and Cartilage Regeneration, we are researching and developing the treatment of osteoarthritis using human adipose stem cells (ASCs) from the renewal of the department in 2018. To clarify the protective effects of human ASCs for cartilage more precisely, we are planning to establish the assay system for the knee pain of mouse. We are also developing the culture medium by which highly-functional human mesenchymal cells can be amplified stably and effectively. We are also working on basic research for (1) elucidation of molecular mechanisms underlying osteoarthritis (2) clarification of the roles of tissue stem cells in the homeostasis of joints and pathogenesis of osteoarthritis.

In the Department of Tissue Stem Cells/ Life Dental Science, we are conducting research on the development of cleft lip and palate treatment methods using human dental pulp stem cells and human umbilical cord. In addition, we are conducting research into airway reconstruction using human ES cells and developing techniques to strengthen airway anastomoses using cytokines, and also working on research into gingival regeneration using mold-encapsulated tissues.

In the Department of Eat-Loss Medicine, in order to support "eating," which is the foundation of human life, we are conducting research to systematize the diagnosis, prevention, and treatment of "eating" as an academic discipline by approaching the problem of persistent inability to eat from the oral region, so that many people can live a full, healthy life.

In the Department of Clinical Stem Cell Biology, we are conducting research for the development of a cell therapy for the peri-implantitis. In addition, to produce regenerated cartilage and bone with high safety and usefulness, to realize production system and establish practical quality control and to promote the application of regenerated cartilage and bone, we are conducting research on development of novel scaffolds in cartilage and bone regeneration, development of 3-D reconstruction system for regenerated tissues, evaluation on biochemical and biophysical properties of regenerated tissues in vivo and clinical trials and application of regenerated cartilage and bones.

Clinical Studies

Of particular note is clinical studies started as a result of basic research. In Department of Bone & Cartilage Regenerative Medicine, a clinical study on bone implants into non-loading parts (IRB approval number #1310) was conducted on 10 patients successfully and a large-scale clinical trial was started across the nation. In project for cartilage regeneration, an investigator-initiated clinical trial "A clinical trial for the validation of safety and efficacy of the implant-type tissue-engineered cartilage using autologous cells" was carried out. In addition, cell therapy was performed on the first patient in a clinical study "a clinical study for the treatment of osteoarthritis of temporomandibular joint by autologous adipose-derived stem cell (AUASC-TKY2017)". Furthermore, preparations are underway in cooperation with the Department of Plastic Surgery at Sapporo Medical University to conduct a clinical study on ear formation using regenerative cartilage for microtia, titled "Auricular regeneration using a new artificial ear (hybrid artificial ear) made from collagenase surface-treated autologous cartilage tissue and biodegradable plastic (NA8150005)."

As stated above, we are proceeding translational research aiming at clinical application of tissue engineering and regenerative medicine. Contribution to the Hospital

Contribution to the Hospital

Division of Tissue Engineering, as a cooperative research facility in the Hospital, opens expensive special machines that each laboratory cannot afford to equip with, such as a confocal laser scanning microscope and a cell analyzer to the Hospital staff, letting them use with cost sharing. Various departments are conducting research using this facility.

References

1. Involvement of Impaired Angiogenesis and Myelosuppression in Antiresorptive-agent Related Osteonecrosis of the Jaw Mouse Model. Igarashi H, Nishizawa S, Miyamoto T, Hikita A, Hoshi K. Tokai J Exp Clin Med. 2023 Apr 20;48(1):22-31.
2. Effect of the Correction of Bilateral Differences in Masseter Muscle Functional Pressure on the Mandible of Growing Rats. Mizuno S, Matsunaga S, Kasahara N, Kasahara M, Shimoo Y, Abe S, Nakano T, Ishimoto T, Hikita A, Nojima K, Nishii Y. J Funct Biomater. 2023 Aug 21;14(8):435.
3. Subcutaneously Transplanted Fresh Cartilage in Allogeneic and Xenogeneic Immunocompetent Mouse. Uto S, Hikita A, Mori D, Sakamoto T, Yano F, Ohba S, Saito T, Takato T, Hoshi K. Tissue Eng Part A. 2023 Oct;29(19-20):541-556.
4. Lipoaspirate stored at a constant low temperature by electric control suppresses intracellular metabolism and maintains high cell viability. Inaki R, Sato Y, Nakamura D, Aikawa Y, Takato T, Hoshi K, Hikita A. Regen Ther. 2023 Nov 21; 24:662-669.
5. Transcriptional reprogramming during human osteoclast differentiation identifies regulators of osteoclast activity. Hansen MS, Madsen K, Price M, S   K, Omata Y, Zaiss MM, Gorvin CM, Frost M, Rauch A. Bone Res. 2024 Jan 24;12(1):5.
6. Changes in knee joint destruction patterns among patients with rheumatoid arthritis undergoing total knee arthroplasty in recent decades. Takeda R, Matsumoto T, Omata Y, Inui H, Taketomi S,

Nagase Y, Nishikawa T, Oka H, Tanaka S. Clin Rheumatol. 2023 Sep;42(9):2341-2352.

The Tokai J Exp Clin Med. 2023;48(2):67-71.

7. Associated correction of forefoot alignment with hindfoot fusion for pes planovalgus deformity. Matsumoto T, Takeda R, Uchio A, Mizuhara H, Omata Y, Juji T, Tanaka S. Foot Ankle Surg. 2023 Apr;29(3):280-287.
8. Platysma bands are associated with laryngeal penetration in older adults with suspected dysphagia. Tonosaki K, Yonenaga K, Itai S, Ono S, Oyama S, Mizuno T, Watanabe R, Hoshi K. Japanese Journal of Hospital General Medicine 2023 5-6 217-225.
9. Saturation of percutaneous oxygen decreases with meal consumption in patients with acute pneumonia. Tonosaki K, Yonenaga K, Ono S, Itai S, Oyama S, Mizuno T, Watanabe R, Hoshi K. The Tokai Journal of Experimental and Clinical Medicine. 2023 48(4) 123-127.
10. The inhibitory effect of catechin on the growth of oral bacteria in vitro and halitosis in a clinical setting. Itai S, Tonosaki K, Ono S, Watanabe R, Koshino K, Hoshi K, Yonenaga K. Oral care. 2023 18(1) 27-33.
11. Understanding the amount of dietary fluid that can be easily swallowed. Itai S, Tonosaki K, Ono S, Watanabe R, Hoshi K, Yonenaga K. Journal of Oral and Medical Science. 2023 1(3) 1-3.
12. Health effects of catechin in the daily intake of green tea. Itai S, Yonenaga K, Ono S, Tonosaki K, Watanabe R, Hoshi K. Journal of Oral and Medical Science. 2023 1(2) 1-10.
13. Pre-market survey for thickened green tea prototypes. Yonenaga K, Itai S, Tonosaki K, Ono S, Watanabe R, Tsubo R, Hoshi K. Journal of Oral and Medical Science. 2024 2(6) 1-4.
14. Weight loss and functional decline in older Japanese people: A cohort study using large-scale claims data. Ono S, Sasabuchi Y, Yamana H, Yokota I, Okada A, Matsui H, Itai S, Yonenaga K, Tonosaki K, Watanabe R, Ono Y, Yasunaga H, Hoshi K. Archives of Gerontology and Geriatrics. 2024 120(105354).
15. First Application of Intraumbilical Longitudinal Incision to Pyloromyotomy for Hypertrophic Pyloric Stenosis. Suzuki K, Komura M, Satake R, Terawaki K, Kodaka T, Gohara T, Yonekawa H.

【Book】

Cooperative Unit of Medicine and Engineering Research

Organization

The University of Tokyo Hospital

Cardiovascular Medicine, Nutrition and Metabolism, Surgical Oncology, Vascular Surgery, Artificial Organ and Transplantation, Cardiac Surgery, Thoracic Surgery, Neurosurgery, Urology, Orthopaedic Surgery, Oral and maxillofacial Surgery, Radiology, Tissue Engineering Unit, Department of Clinical Epidemiology & Systems, Bone & Cartilage Regenerative Medicine, Cartilage of Bone Regeneration, Department of Immunotherapeutics (Medinet), Division of Science for Joint Reconstruction

Engineering and Pharmaceutical Research

Chemical System Engineering, Mechanical Engineering, Precision Engineering, Quantum Engineering and System Science, Nuclear Engineering and Management, Chemistry and Biotechnology, Material Engineering, Information Science and Technology, Frontier Sciences, Pharmaceutical Sciences Laboratory of Chemistry and Biology, Center for Disease Biology and Integrative Medicine, Center for Disease Biology and Integrative Medicine Regenerative Medical Engineering, Center for Disease Biology and Integrative Medicine Clinical Biotechnology, Research Center for Advanced Science and Technology, Institute of Industrial Science

※The following information is the same as that of the previous year for certain reasons.

Introduction and Organization

The application of an advanced bioscience to a new technical development of clinical medicine has become an important subject for research in the 21st century. We've established Cooperative Unit of Medicine and Engineering Research at The University of Tokyo Hospital to create a new research and education center, which cross-sectionally unites medicine with engineering research for the development of a next generation medical technology.

2002 June. The establishment of Cooperative Unit of Medicine and Engineering Research was approved

by a hospital administration committee as a special practice unit that belongs to The University of Tokyo Hospital.

2002 September. A steering committee of Cooperative Unit of Medicine and Engineering Research was organized by representative members of relevant clinical departments. The committee made a decision of the following basic principles; recruitment for the participation to this unit should be, as a general rule, an open call for a joint project of clinical department and engineering or pharmaceutical research group in The University of Tokyo, an equipment/administration expense of a laboratory should be a responsibility of

the user, and a basic participation period to this unit should be three years and for the continued participation in the unit, a review and approve of the steering committee is indispensable.

2002 October. An open call for participants to this unit started. There were 18 applications and the steering committee approved all projects after review. A liaison conference of Cooperative Unit of Medicine and Engineering Research was organized by a representative member of each project. Configuration of each project in a space of 554.4m² that is consisted of a portion of the first floor and the basement of an administration building came to a decision by the conference.

2003 May. The construction of Cooperative Unit of Medicine and Engineering Research was completed. The cost of the construction was shared by the participation groups.

2003 May 22. The first research meeting of Cooperative Unit of Medicine and Engineering Research took place and research activities started.

2004 September 3. The second research meeting of Cooperative Unit of Medicine and Engineering Research took place.

2005 September 13. The third research meeting of Cooperative Unit of Medicine and Engineering Research took place.

2006 December 21. The fourth research meeting of Cooperative Unit of Medicine and Engineering Research took place.

2007 December 13. The fifth research meeting of Cooperative Unit of Medicine and Engineering Research took place.

2009 December 3. The sixth research meeting of Cooperative Unit of Medicine and Engineering Research took place.

2011 February 2. The seventh research meeting of Cooperative Unit of Medicine and Engineering Research took place.

2011 December 17. The eighth research meeting of Cooperative Unit of Medicine and Engineering Research took place

2013 January 25. Development forum of advanced medical seeds took place

2014 January 24. Development forum of advanced medical seeds took place

2015 January 22. Development forum of advanced

medical seeds took place

2016 February 2. Development forum of advanced medical seeds took place

2017 February 2. Development forum of advanced medical seeds took place

2018 February 1. Development forum of advanced medical seeds took place

2018 October. Each lab was moved from the the first floor and the basement of an administration building, based on the decision of redistribution of hospital facility

2019 February 18. Development forum of advanced medical seeds took place

2020 January 21. Development forum of advanced medical seeds took place

2021 February 10. Development forum of advanced medical seeds took place

2022 February 4. Development forum of advanced medical seeds took place

Research activities

Development of Advanced Stereotactic Radiation Cancer Therapy System

Department of Radiology

Nuclear Professional School, Department of Nuclear Engineering and Management

Department of Chemical System Engineering

High Precision Stereotactic X-ray Cancer Therapy System. Development of Advanced Compact Electron Linear Accelerator for Cancer Inspection and Therapy
The aim of this research is to apply the in-vivo visualization technique developed by our group in high-precision radiation therapy and to develop the motion prediction system for a real-time tumor-tracking radiation therapy. For the visualization of the treatment area during treatment, a four-dimensional cone-beam computed tomography (4D CBCT) reconstruction algorithm is developed by taking the anatomy or tumor motion analysis into account. In-treatment 4D CBCT requires the projection images acquired during treatment. The projection images are analyzed online, and compared with the reprojection images from the treatment planning CT or registration CT. The time lag due to the analysis can be compensated by the prediction using a multi-channel singular spectrum analysis. This

system will remove a delay problem during the real-time tumor-tracking radiation therapy, and will provide a safer radiation therapy than the current ones because this will be able to detect an irregular breathing motion of the tumor.

Research and development of micro-neurosurgical robotic systems

Department of Neurosurgery, The University of Tokyo Hospital

Mitsubishi Laboratory, Department of Mechanical Engineering, School of Engineering

Development of micro-neurosurgical robotic systems and advanced microscopic image processing for autonomous surgical task recognition.

Development of Support Systems for Risk Reduction in the Clinical Process

Chemical System Engineering

Center for Epidemiology and Preventive Medicine

Our specific targets are research and education on the integration of biological and clinical information including genome. In particular, we focus on establishment of personalized medicine as translational research, selection of drug targets by proteomics, interpretation of transcriptional regulations and drug development by targeting transcriptional factors in metabolic and cardiovascular diseases. Also, analyses of genomic functions, clinical safety monitoring by clinical database and assessments of clinical information systems are conducted.

Project of Neutron Capture Therapy & Innovation of DDS for Cancer

Department of Cardiothoracic Surgery, Graduate School of Medicine

Institute of Engineering Innovation, School of Engineering

Department of Bioengineering, School of Engineering

In order to control and eliminate human cancers, we develop the neutron capture therapy (NCT) using small neutron accelerator equipped to hospital and also aim to augment cancer therapy combined with approaches of Drug Delivery System. We develop the tumour specific drug delivery systems entrapped boron or gadolinium compounds as neutron capture

agents (WOW emulsion, Nano-micelle, Cationic Polyplex).

Development of adhesion barrier materials using a new animal model of liver-peritoneal adhesion

Artificial Organ and Transplantation Division, Department of Surgery, Graduate School of Medicine, University of Tokyo

Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, University of Tokyo

Organs and Biosystems Engineering Laboratory, Institute of Industrial Science, The University of Tokyo
Division of Biomedical Equipment and Biomaterials, Center for Disease Biology and Integrative Medicine, Graduate School of Medicine, The University of Tokyo
Department of Chemical System Engineering, Graduate School of Engineering, The University of Tokyo

Department of Bioengineering, Graduate School of Engineering, The University of Tokyo

Adhesions between liver and other organs are an important issue in the cases of second surgeries such as hepatic resection. Adhesions extend operative duration; in addition, they increase the risk of surgeries. Thus, it is important to avoid adhesions at a first surgery. However, no one report both the animal model and adhesion barrier materials of liver adhesion. We try to develop a new adhesion model by hepatic resection, instead of a usual peritoneal abrasion model. Also, we develop new materials for preventing the adhesions.

Development of gene therapy of cardiovascular therapy by polymeric micelles.

Department of Vascular Surgery, Division of Tissue Engineering, The University of Tokyo Hospital

Kataoka Laboratory, Department of Materials Science and Engineering, Graduate School of Engineering, The University of Tokyo

To achieve effective and safe in vivo gene therapy of cardiovascular and vascular diseases, we are developing non-viral gene vectors based on nano-scaled polymer assemblies (polymeric micelles). Polymeric micelles, which are spontaneously formed from block copolymers, have a core containing packaged genes surrounded by biocompatible poly

(ethylene glycol) (PEG) palisades, and a variety of pilot molecules can be installed on the surface of polymeric micelles. This "virus-mimicking" nanoparticles might achieve efficient gene transfer to the targeted tissues or cells because of protection of the loaded DNA from nuclease attack, their lowered non-specific interaction with proteins and cells and facilitated internalization by the targeted cells through specific interaction of the pilot molecules. Currently, our research has been focused on in vivo gene transfer to artery walls and muscles using polymeric micelles incorporated genes.

References (in 2021)

1. Hanada K, Hoshina K, Iwakiri T, Akai T, Miyahara K, Isaji T, Takayama T, Yamamoto S. A comparison of subjective clinical and objective judgement of abdominal aortic aneurysm morphology. *Int Angiol* 2021;40:138-142.
2. Okata S, Hoshina K, Miyahara K, Matsukura M, Akai T, Isaji T, Takayama T. High aneurysm wall enhancement values are associated with late sac shrinkage after endovascular repair of abdominal aortic aneurysms. *Medicine(Baltimore)* 2021 Jan 15;100:e24133.
3. Hoshina K, Kato M, Ishimaru S, Michihata N, Yasunaga H, Komori K; Japanese Committee for Stentgraft Management (JACSM). Impact of the urgency and the landing zone on rates of in-hospital death, stroke, and paraplegia following thoracic endovascular aortic repair in Japan. *J Vasc Surg* 2021; S0741-5214(21)00142-7
4. Matsuura S, Takayama T, Yuhn C, Oshima M, Shirasu T, Akai T, Isaji T, Hoshina K. Carotid stump pressure and contralateral internal carotid stenosis ratio during carotid endarterectomies: 1D-0D hemodynamic simulation of cerebral perfusion. *Ann Vasc Dis* 2021;14:39-45.
5. Hoshina K, Komori K, Kumamaru H, Shimizu H. The Outcomes of endovascular aneurysm repair in Japan in 2017: A Report from the Japanese Committee for Stentgraft Management. 2021;25; 14:92-98.
6. Sugawara M, Hoshina K, Chigira M, Suzuki H, Daimon M, Takayama T, Ono Y, Yatomi Y. Usefulness of duplex ultrasonography to detect collagen sponge misplacement into the arterial lumen during the use of Angio-Seal: A case report. *SAGE Open Med Case Rep* 2021;9: 2050313X211004818
7. Matsuura S, Takayama T, Oyama TG, Oyama K, Taguchi M, Endo T, Akai T, Isaji T, Hoshina K. A Radiation-crosslinked gelatin hydrogel that promotes tissue incorporation of an expanded polytetrafluoroethylene vascular graft in rats. *Biomolecules* 2021;11:1105.
8. Iida T, Muroto K, Shiratori H, Nozawa H, Kawai K, Sasaki K, Emoto S, Kishikawa J, Ishii H, Yokoyama Y, Abe S, Nagai Y, Anzai H, Sonoda H, Takayama T, Hoshina K, Ishihara S. Impact of inferior mesenteric artery occlusion on the calibre of collateral arteries of the colon. *Anticancer Res* 2021;41: 5189-5193.
9. Hoshina K, Komori K, Kumamaru H, Shimizu H. The outcomes of thoracic endovascular aortic repair in Japan in 2017: A report from the Japanese Committee for Stentgraft Management. *Ann Vasc Dis* 2021;14:281-288.
10. Mo M, Hirokawa M, Satokawa H, Yasugi T, Yamaki T, Ito T, Onozawa S, Kobata T, Shirasugi N, Shokoku S, Sugano N, Sugiyama S, Hoshina K, on behalf of guideline committee Japanese Society of Phlebology, Ogawa T, on behalf of guideline committee of endovenous treatment for varicose veins. Supplement of clinical practice guidelines for endovenous thermal ablation for varicose veins: Overuse for the inappropriate indication. *Ann Vasc Dis* 2021;14:323-327.
11. Horio K, Marinho MM, Harada K, Muto J, Nakatomi H, Saito N, Morita A, Watanabe E, Mitsusishi M. "The effects of Grid Size for Automatic Suture Thread, Detection with an Image Classifier", The 17th Asian Conference on, Computer Aided Surgery (ACCAS2021), pp.102-103, Online, December 10, 2021.
12. Arvind K. Chandel S, Shimizu A, Hasegawa K, Ito T. "Advancement of biomaterial-based postoperative adhesion barriers" *Macromolecular Bioscience*, 2021, 2000395 DOI:10.1002/mabi.202000395
13. 大木悠一朗、伊藤大知 “「生体直交型反応を用いたインジェクタブルハイドロゲル」” *日本薬学会誌ファルマシア*, 2021, 57(11), 1025-

1029 https://doi.org/10.14894/faruawpsj.57.11_1025

14. Yanagie H, Fujino T, Yanagawa M, Terao T, Imagawa T, Fujihara M, Morishita Y, Mizumachi R, Murata Y, Dewi N, Ono Y, Ikushima I, Seguchi K, Nagata M, Nonaka Y, Furuya Y, Hisa T, Nagasaki T, Arimori K, Nakashima T, Sugihara T, Kakimi K, Ono M, Nakajima J, Eriguchi M, Higashi S, Takahashi H.: Tumor Growth Suppression With Novel Intra-arterial Chemotherapy Using Epirubicin-entrapped Water-in-oil-in-water Emulsion In Vivo.. *In Vivo*. 2021 Jan-Feb;35(1): 239-248. doi:10.21873/invivo.12252. PMID: 33402470
15. Yanagie H, Yanagawa M, Morishita Y, Shinohara A, Dewi N, Nonaka Y, Furuya Y, Mizumachi R, Murata Y, Nakamura H, Suzuki M, Sakurai Y, Tanaka H, Masunaga S, Ono K, Sugihara T, Nashimoto M, Yamauchi H, Ono M, Nakajima J, Takahashi H. : Suppression of Tumor Growth in a Rabbit Hepatic Cancer Model by Boron Neutron Capture Therapy With Liposomal Boron Delivery Systems. *In Vivo*. 2021 Nov-Dec;35(6):3125-3135. doi: 10.21873/invivo.12607. PMID: 34697143

Genomic Research Support Center (GresCent)

Director & Professor

Yutaka Osuga, M.D., Ph.D.

1. Organization

Genomic Research Support Center was established in 2017 to support appropriate and harmonious achievements of advanced genomic researches at the University of Tokyo Hospital. Genomic Research Support Center deals with cancer, life-style disease, hereditary disorders, and so on. This center is directed by Professor Yutaka Osuga. Experts of these fields, including Associate Professor Nobuhiro Shojima, participate in the activities as follows; (1) large scale analysis of genomes utilizing next generation sequencers and establishment of pipelines of genome informatic analysis, (2) elucidation of hereditary factors and pathogenesis of various diseases, (3) integrated research and education of genomic and clinical information, (4) analysis of polymorphism and mutation of genes involved in susceptibility and response to treatment in various diseases such as life-style disease, and (5) establishment of database and integrated data mining of associated clinical information.

2. Activities

In collaboration with RIKEN, we have identified genetic variations conferring susceptibility to type 2 diabetes, myocardial infarction and renal dysfunction in the Japanese population from the genome-wide association study (GWAS) results. We identified type 2 diabetes - associated loci, including missense variants in genes related to insulin secretion (GLP1R). To examine type 2 diabetes risk in individuals, our team carried out a meta-analysis of GWAS data. We identified loci that are newly implicated in

predisposition to type 2 diabetes. (medRxiv [Preprint]. 2023 Mar 31, Nature, 2024, 627, 347-357).

In collaboration with the Osaka University, RIKEN and BioBank Japan, we assembled an ancestrally diverse collection of GWAS of type 2 diabetes through the UK Biobank, AGEN T2D and the Diabetes Meta-Analysis of Trans-Ethnic association studies (DIAMANTE) Consortium. Multi-ancestry GWAS meta-analysis identified multiple loci attaining stringent genome-wide significance, which were delineated to multiple distinct association signals. As expected, ancestry-specific genetic risk score (GRS) performed best in test GWAS from their respective ancestry group. Multi-ancestry meta-analysis maximizes power to detect association signals that are shared across ancestry groups. By modeling heterogeneity in allelic effects across ancestries, our meta-regression approach can also allow for association signals that are driven by ancestry-specific causal variants, although power will be limited by the sample size available in that ancestry group.

In collaboration with the Osaka University, RIKEN and BioBank Japan, we profiled serum metabolites of persons with type 2 diabetes with both diabetic retinopathy and diabetic kidney diseases using a comprehensive non-targeted metabolomics approach with mass spectrometry. We compared the abundance of the serum metabolites between the persons with type 2 diabetes with multiple complications and without any complications, identifying five metabolites, including N-acetylneuraminic acid significantly increased in those with the complications (Commun Med. 2023, 9;3(1):5). Our metabolome

analysis identified the serum metabolite features of the persons with type 2 diabetes with the complications, which could potentially be used as biomarkers.

We conducted whole genome sequence and analyzed the sequence data of over 2,000 subjects with type 2 diabetes in collaboration with the Osaka University, RIKEN and BioBank Japan. We are developing the methods to predict diabetic complications and deterioration of diabetes by bioinformatics algorithms including the Penalized regression method, often used in machine learning and public OmiX database.

In collaboration with Department of Clinical Genomics, we supported the meetings and expert-panel regarding cancer and rare diseases. We had clinical and genomic WEB conference with hospitals related to cancer treatment.

We shared genomic and metabolome data with researchers about type 2 diabetes association study, through national bioscience database center, NBDC (<https://humandbs.biosciencedbc.jp>).

We made paper to inform for the participants of the research on ‘Realization of personalized medicine for Metabolic syndrome related disease.’ in collaboration with research ethics support center.

We used panel analysis applying next-generation sequencer, AI supported prediction of 3-dimensional protein structure, and revealed the genetic diagnosis on extreme phenotypes of diseases related to lifestyles including, maturity onset diabetes of the young and lipodystrophy and predicted the prognosis and selected effective therapies.

3. References

- 1: Tomofuji Y, Suzuki K, Kishikawa T, Shojima N, Hosoe J, Inagaki K, Matsubayashi S, Ishihara H, Watada H, Ishigaki Y; BioBank Japan Project; Inohara H, Murakami Y, Matsuda K, Okada Y, Yamauchi T, Kadowaki T. Identification of serum metabolome signatures associated with retinal and renal complications of type 2 diabetes. *Commun Med (Lond)*. 2023 Jan 9;3(1):5. doi: 10.1038/s43856-022-00231-3. PMID: 36624208; PMCID: PMC9829655.
- 2: Kusakabe M, Taguchi A, Tanikawa M, Wagatsuma R, Yamazaki M, Tsuchimochi S, Toyohara Y, Kawata A, Baba S, Ueno T, Sone K, Mori-Uchino M, Ikemura M, Matsunaga H, Nagamatsu T, Wada-Hiraike O, Kawazu M, Ushiku T, Takeyama H, Oda K, Kawana K, Mano H, Osuga Y. Cells with stem-like properties are associated with the development of HPV18-positive cervical cancer. *Cancer Sci*. 2023 Mar;114(3):885-895. doi: 10.1111/cas.15664. Epub 2022 Dec 9. PMID: 36404139; PMCID: PMC9986059.
- 3: Shojima N, Yamauchi T. Progress in genetics of type 2 diabetes and diabetic complications. *J Diabetes Investig*. 2023 Apr;14(4):503-515. doi: 10.1111/jdi.13970. Epub 2023 Jan 14. PMID: 36639962; PMCID: PMC10034958.
- 4: Suzuki K, Hatzikotoulas K, Southam L, Taylor HJ, Yin X, Lorenz KM, Mandla R, Huerta-Chagoya A, Rayner NW, Bocher O, Ana Luiza de SVA, Sonehara K, Namba S, Lee SSK, Preuss MH, Petty LE, Schroeder P, Vanderwerff B, Kals M, Bragg F, Lin K, Guo X, Zhang W, Yao J, Kim YJ, Graff M, Takeuchi F, Nano J, Lamri A, Nakatochi M, Moon S, Scott RA, Cook JP, Lee JJ, Pan I, Taliun D, Parra EJ, Chai JF, Bielak LF, Tabara Y, Hai Y, Thorleifsson G, Grarup N, Sofer T, Wuttke M, Sarnowski C, Gieger C, Nounsime D, Trompet S, Kwak SH, Long J, Sun M, Tong L, Chen WM, Nongmaithem SS, Noordam R, Lim VJY, Tam CHT, Joo YY, Chen CH, Raffield LM, Prins BP, Nicolas A, Yanek LR, Chen G, Brody JA, Kabagambe E, An P, Xiang AH, Choi HS, Cade BE, Tan J, Elaine Broadaway K, Williamson A, Kamali Z, Cui J, Adair LS, Adeyemo A, Aguilar-Salinas CA, Ahluwalia TS, Anand SS, Bertoni A, Bork-Jensen J, Brandslund I, Buchanan TA, Burant CF, Butterworth AS, Canouil M, Chan JCN, Chang LC, Chee ML, Chen J, Chen SH, Chen YT, Chen Z, Chuang LM, Cushman M, Danesh J, Das SK, Janaka de Silva H, Dedoussis G, Dimitrov L, Doumatey AP, Du S, Duan Q, Eckardt KU, Emery LS, Evans DS, Evans MK, Fischer K, Floyd JS, Ford I, Franco OH, Frayling TM, Freedman BI, Genter P, Gerstein HC, Giedraitis V, González-Villalpando C, González-Villalpando ME, Gordon-Larsen P, Gross M, Guare LA, Hackinger S, Han S,

- Hattersley AT, Herder C, Horikoshi M, Howard AG, Hsueh W, Huang M, Huang W, Hung YJ, Hwang MY, Hwu CM, Ichihara S, Ikram MA, Ingelsson M, Islam MT, Isono M, Jang HM, Jasmine F, Jiang G, Jonas JB, Jørgensen T, Kandeel FR, Kasturiratne A, Katsuya T, Kaur V, Kawaguchi T, Keaton JM, Kho AN, Khor CC, Kibriya MG, Kim DH, Kronenberg F, Kuusisto J, Läll K, Lange LA, Lee KM, Lee MS, Lee NR, Leong A, Li L, Li Y, Li-Gao R, Lithgart S, Lindgren CM, Linneberg A, Liu CT, Liu J, Locke AE, Louie T, Luan J, Luk AO, Luo X, Lv J, Lynch JA, Lyssenko V, Maeda S, Mamakou V, Mansuri SR, Matsuda K, Meitinger T, Metspalu A, Mo H, Morris AD, Nadler JL, Nalls MA, Nayak U, Ntalla I, Okada Y, Orozco L, Patel SR, Patil S, Pei P, Pereira MA, Peters A, Pirie FJ, Polikowsky HG, Porneala B, Prasad G, Rasmussen-Torvik LJ, Reiner AP, Roden M, Rohde R, Roll K, Sabanayagam C, Sadow K, Sankareswaran A, Sattar N, Schönherr S, Shahriar M, Shen B, Shi J, Shin DM, Shojima N, Smith JA, So WY, Stančáková A, Steinthorsdottir V, Stilp AM, Strauch K, Taylor KD, Thorand B, Thorsteinsdottir U, Tomlinson B, Tran TC, Tsai FJ, Tuomilehto J, Tusie-Luna T, Udler MS, Valladares-Salgado A, van Dam RM, van Klinken JB, Varma R, Wachter-Rodarte N, Wheeler E, Wickremasinghe AR, van Dijk KW, Witte DR, Yajnik CS, Yamamoto K, Yamamoto K, Yoon K, Yu C, Yuan JM, Yusuf S, Zawistowski M, Zhang L, Zheng W; VA Million Veteran Program, AMED GRIFIN Diabetes Initiative Japan; Project B1, BioBank PM, Center RG, Consortium E; International Consortium for Blood Pressure (ICBP); Meta-Analyses of Glucose and Insulin-Related Traits Consortium (MAGIC); Raffel LJ, Igase M, Ipp E, Redline S, Cho YS, Lind L, Province MA, Fornage M, Hanis CL, Ingelsson E, Zonderman AB, Psaty BM, Wang YX, Rotimi CN, Becker DM, Matsuda F, Liu Y, Yokota M, Kardia SLR, Peyser PA, Pankow JS, Engert JC, Bonnefond A, Froguel P, Wilson JG, Sheu WHH, Wu JY, Geoffrey Hayes M, Ma RCW, Wong TY, Mook-Kanamori DO, Tuomi T, Chandak GR, Collins FS, Bharadwaj D, Paré G, Sale MM, Ahsan H, Motala AA, Shu XO, Park KS, Jukema JW, Cruz M, Chen YI, Rich SS, McKean-Cowdin R, Grallert H, Cheng CY, Ghanbari M, Tai ES, Dupuis J, Kato N, Laakso M, Köttgen A, Koh WP, Bowden DW, Palmer CNA, Kooner JS, Kooperberg C, Liu S, North KE, Saleheen D, Hansen T, Pedersen O, Wareham NJ, Lee J, Kim BJ, Millwood IY, Walters RG, Stefansson K, Goodarzi MO, Mohlke KL, Langenberg C, Haiman CA, Loos RJJ, Florez JC, Rader DJ, Ritchie MD, Zöllner S, Mägi R, Denny JC, Yamauchi T, Kadowaki T, Chambers JC, Ng MCY, Sim X, Below JE, Tsao PS, Chang KM, McCarthy MI, Meigs JB, Mahajan A, Spracklen CN, Mercader JM, Boehnke M, Rotter JI, Vujkovic M, Voight BF, Morris AP, Zeggini E. Multi-ancestry genome-wide study in >2.5 million individuals reveals heterogeneity in mechanistic pathways of type 2 diabetes and complications. *medRxiv* [Preprint]. 2023 Mar 31: 2023.03.31.23287839. doi: 10.1101/2023.03.31.23287839. PMID: 37034649; PMCID: PMC 10081410.

BioResource Center

Director

Tetsuo Ushiku, M.D., Ph.D. (Professor, Department of Pathology and Diagnostic Pathology)

Deputy Director

Katsutoshi, Oda, M.D., Ph.D. (Professor, Division of Integrative Genomics)

Staff

Aya Shinozaki-Ushiku, M.D., Ph.D. (Associate Professor, Division of Integrative Genomics)

Homepage <https://www.h.u-tokyo.ac.jp/patient/depts/bio-resource/>

Introduction and Organization

A wide variety of clinical and scientific research is being conducted at The University of Tokyo Hospital and Faculty of Medicine. When using samples obtained from patients through surgery and laboratory tests, researchers of each department have obtained informed consent for the research and stored the samples in their own laboratory. To utilize valuable resources more effectively, the center specialized in collecting and storing samples is needed. The University of Tokyo Hospital is one of the core hospitals to promote cancer genomic medicine in Japan and is required to equip biobank to store tissue samples of multiple organs.

In these settings, a working group has started to work on the establishment of BioResource Center since 2020. Members from the Departments of Clinical Genomics, Pathology, Clinical Laboratory and Surgery, as well as experts in basic medical research, discussed how to inform and obtain consent of the patients, details of tissue sampling and storing protocols, and the process of utilizing samples in medical research. After the approval by Hospital Executives, BioResource Center was established as one of the Clinical Research Services of the University of Tokyo Hospital on Apr 1, 2021. This BioResource Center Project was also approved by the Research Ethics Committee of the Faculty of Medicine on Aug 16, 2021.

Samples, clinical information, and research data with written informed consent of the patients are stored in

the center and are utilized in the research approved by the Research Ethics Committee. Staffs of the center and representatives of clinical departments also hold a committee to review the research protocols to check whether the use of the stored samples is appropriate.

Clinical activities

Three doctors (director, deputy director and a staff) and two project academic specialists are in charge of the activity. We work together with the Department of Surgery, Pathology, Clinical Laboratory and Surgical Center in obtaining patients' consent and collecting samples. Members of the Office of Research Support also support us in the management of the center.

In FY2021, we worked on the sampling protocols, developed a system and a database to collect the information of patients' consent and stored samples, and set up a laboratory. Sampling of peripheral blood and tissues started in March 2022. At the end of FY2023, samples from 500 patients were collected and stored. In November 2022, the scheme for medical research using samples stored in BioResource Center was approved by Research Ethics Committee of the Faculty of Medicine, making the researchers in the hospital available for the stored samples.

BioResource Center freezes and stores DNA and plasma extracted from peripheral blood and paired normal/tumor tissues. Sample information such as patient's age, sex and cancer type are also collected.

The center will cover patients of Internal Medicine who suffer from lifestyle diseases and intractable diseases and pediatric patients in the future.

Teaching and Research activities

In FY2023, we offered samples for the whole-genome analysis conducted as a national research project. We hope to expand our activities in research as well as educating specialists on banking methods in the coming year.

References

None

Department of Clinical Research Governance

Director & Project Professor

Junji Moriya, M.D., Ph.D.

Research Associate

Kazuyoshi Ichihashi, Ph.D.

※The following information is the same as that of the previous year for certain reasons.

Website <http://www.h.u-tokyo.ac.jp/english/centers-services/organization/l4/researchgovernance.html>

History and Overview of the Organization

The Department of Clinical Research Governance was established independently from the Clinical Research Support Center on January 1st, 2015, for the management of clinical research. The aim of the department is an appropriate and rapid response to various issues surrounding clinical research in recent years, to prevent problems related to research ethics and research misconduct, and to promote highly reliable clinical research. The intention of the Department of Clinical Research Governance is to establish a system that would enable the University of Tokyo Hospital to take the initiative in managing and promoting clinical research so as to ensure the reliability of clinical research and compliance with the ethics of clinical research promoted by university hospitals providing advanced medical care.

The Department of Clinical Research Governance is now composed of three offices: 1) Office of Strategic Planning and Promotion, 2) Office of Research Integrity and Promotion, and 3) Office of Clinical Compliance. These offices mutually cooperate to promote and strengthen governance functions within the hospital.

The following activities are carried out by the

Office of Strategic Planning and Promotion ; (1) formulating comprehensive strategies for research and development at the University of Tokyo Hospital, (2) adopting the role of administrative headquarters when publicly applying for large-scale research projects, (3) serving as a liaison for consultations regarding the acquisition of research funds and intellectual properties, (4) examination financial self-reliance strategies of the clinical research base, (5) discovering needs and seeds in clinical practice, (6) investigating research activities at the University of Tokyo Hospital and creating a database, (7) collecting clinical research information from external organizations, (8) activities related to conflicts of interest at the University of Tokyo Hospital, (9) clerical work related to the Advanced Medicine Development Support Management Committee, and (10) clerical work related to the Special Clinical Research Steering Committee.

The activities of the Office of Research Integrity and Promotion are as follows; (1) responding to problems related to research ethics and research misconduct, (2) educational activities for clinical researchers; and (3) the dissemination of workshop summaries.

The activities of the Office of Clinical Compliance are as follows; (1) auditing of clinical researches and clinical trials, (2) integrated management of

outsourced auditing, (3) integrated management of audit results of the University of Tokyo Hospital, and (4) educational workshops and guidance related to auditing.

The Department of Clinical Research Governance consists of one director (a full-time post), one Research Associate/URA in the Office of Strategic Planning and Promotion, three staffs (2 auditors and one temporary staffs (an auditor staff) in the Office of Clinical Compliance, and two staffs in the Office of Research Integrity and Promotion as of March 2022.

Activities

The Office of Strategic Planning and Promotion has undertaken the following activities in the fiscal year 2021.

- 1) Coordination of organization for clinical trials/researches; assisting the holding of Specified Clinical Research Steering Committee and the Specified Clinical Research Auditing Committee, and assisting the preparation of reports on clinical research activities as the Clinical Research Core Hospitals under the Medical Care Act (Act No. 205 of July 30, 1948) for surveys conducted by the Ministry of Health, Labor and Welfare (MHLW).
- 2) Others; investigations of research paper publication activities, co-operating the “Forum for Development of Seeds for Advanced Medicine”, etc.

The Office of Clinical Compliance has undertaken the following activities in the fiscal year 2021.

- 1) Audit activities; as regard to trials/researches conducted by the University of Tokyo Hospital, the office conducted a total of eight trials (six audits for investigator-initiated clinical trials, and two audits for Specified Clinical Researches).
- 2) Consolidating information; the office collected all the information on audit results including directly outsourced by principal investigators, and has been centrally managing the GCP inspections findings conducted at the University of Tokyo Hospital.
- 3) Preparing documents; the office prepared documents of SOP in general auditing, templates for auditing of each trial, start-up meetings, and protocols, along with maintenance of existing checklists.

- 4) MHLW program for educational workshops and guidance related to auditing; the office has a central role in performing workshops in the fiscal year 2021, and held a beginners workshop in September 2nd and 3rd, and a mid-career workshop in November 18th and 19th.

The Office of Research Integrity and Promotion has undertaken the following activities in the fiscal year 2021.

- 1) Collecting and disseminating information for clinical quality assurance; the office has sent a total of six e-mails for all personnel in the University of Tokyo Hospital, along with disclosing a total of 16 information in the website of the Department of Clinical Research Governance.
- 2) Educational activities for clinical researchers; the office has held an e-learning seminar regarding to the management of conflict of interest and quality assurance in clinical researches (there were 1935 participants in a Step1 seminar, and 1888 participants in a Step2 seminar).
- 3) Promotion of activities for research integrity; the office has engaged in creating a team for supporting activities regarding to QMS in investigator-initiated clinical trials conducted in the University of Tokyo Hospital. The team consists of members of the Office of Research Integrity and Promotion, and the Clinical Research Promotion Center. The team extracted problems and points to consider as to working flows of collecting and reporting information for deviations or misconducts of clinical trials performed in the University of Tokyo Hospital.

Department of Healthcare Information Management

Professor

Kazuhiko Ohe, M.D.,Ph.D.

Associate Professor

Kayo Waki, M.D.,Ph.D. Yoshimasa Kawazoe, M.D.,Ph.D.

Lecturer

Shinichiro Yokota, PHN,RN,Ph.D., Hidenao Atarashi BMET, Ph.D.

※The following information is the same as that of the previous year for certain reasons.

Homepage <http://www.m.u-tokyo.ac.jp/medinfo/>

Introduction and Organization

In order for the University of Tokyo Hospital to respond strategically and quickly to various changes in the medical system and changes in the university hospital organization, and to operate by making maximum use of medical information, In 2003, the hospital management support departments, which had been separated into the Central Medical Information Department, New Hospital Development Planning Office (hospital measures), Management Improvement Planning Office (hospital measures), Medical Affairs Division, and Administration Division, were integrated and established in 2003. It was newly established in April 2013. The predecessor of the Central Medical Information Department was the Information Processing Department, which was established at the University of Tokyo Hospital in 1975 as an in-hospital measure. In 1983, the Ministry of Education (at that time) officially established the Central Medical Information Department as one of the central medical facilities of the University of Tokyo Hospital.

At the same time, it became possible to accept doctoral course students as the first graduate school of basic medicine. The first professor and director of the Central Medical Information Department was Shigemasa Kaihara (deceased), who established medical

informatics in Japan, and is currently the second generation. In 1997, Professor 1 and Assistant Professor 1, who had been affiliated with the Central Medical Information Department, began to focus on graduate school, and in 2003, as mentioned above, it became the Planning Information Management Department. For the relationship with the Graduate School of Medical Informatics, please refer to the Medical Informatics section of the Department of Social Medicine.

In addition to procuring, developing, implementing, and operating general hospital information systems and comprehensive medical information network systems centered on electronic medical record systems, the Planning Information Management Department also handles systems that support clinical research and medical safety management. We are currently developing a system for this purpose. In addition to strategically managing and analyzing information throughout the hospital and providing operational support based on this information, the hospital is also responsible for formulating mid- to long-term plans, supporting their implementation, and coordinating plans.

Activities

Regarding medical information systems, we updated the system in fiscal year 2017 (2017/12/28-2018/01/04) and updated our unique ordering system and electronic system, which we have been using since 1994 and have continued to improve and update. We stopped using the medical record system and updated it to the Fujitsu EgMAING-GX series package system. As it was a complete system update, there were some difficulties with data migration, and operations were disrupted at the beginning of the update, but it took several months to get things under control and up and running.

In addition, we have been participating in the project as a cooperating organization of MID-NET, a medical information database infrastructure development project that is a joint project between the Pharmaceutical and Food Bureau of the Ministry of Health, Labor and Welfare and PMDA. We have started taking orders.

In addition, the national university hospital disaster medical data backup system, which has been in operation since 2014, continued to be operated by our department as the main care department in 2017, and was completely updated in 2019.

A medical human resources development project managed by the Ministry of Education, Culture, Sports, Science and Technology began in the middle of 2017, and faculty members from this department (Specially Appointed Lecturer Ida and Assistant Professor Yamada) are participating in the steering committee to support the promotion of the project. Details are available at <https://hep.m.u-tokyo.ac.jp/cms/>.

The Ministry of Education, Culture, Sports, Science and Technology's Human Resources Development Project for Utilizing Medical Real Data began in 2019, and Miyake and Kubota were hired as specially appointed assistant professors in this department, and are in charge of curriculum creation and management together with Seki, the assistant professor in charge. Lectures and practical training are mainly held on Saturdays as part of the adult education course, and details can be found at <https://www.med-rwd.jp/>.

Research activities

Please refer to the Department of Social Medicine and Medical Informatics.

University Hospital Medical Information Network (UMIN) Center

Professor

Takahiro Kiuchi, M.D., Ph.D.

Associate Professor

Tsuyoshi Okuhara, Ph.D., M.P.H.

Instructor

Hiroko Okada, R.N., Ph.D., M.P.H.

Eiko Goto, R.D., Ph.D., M.P.H.

Rie Yokota, Ph.D., M.P.H.

Homepage <http://www.umin.ac.jp/>

Introduction and Organization

The UMIN Center was founded within the Hospital Computer Center, University of Tokyo Hospital, and was officially opened in March 1989. Dr. Tsunetaro Sakurai became an associate professor as the first full-time UMIN staff. The following are the objectives of the UMIN Center, as initially outlined in 1989 (No.6 was added later):

1. Provide up-to-date information for healthcare professionals
2. Promote digitalized communication among health-care professionals
3. Support collaborative projects among university hospitals
4. Support collaborative medical research
5. Standardize data format and support data collection
6. Support medical education and clinical training

The original UMIN system utilized an N1 protocol, which was developed in Japan and was the only solution at the time to connect general-use computers of the five major computer vendors in Japan, although

it was poor in function, supporting only line-mode, character-based terminals.

In 1994, we launched a service through the Internet, and it began to spread in those days. The number of UMIN users gradually increased, mainly in the E-mail service.

In 1996, Dr. Takahiro Kiuchi took up a new post while Dr. Sakurai was promoted to professor at Hokkaido University. Dr. Kiuchi updated the system to be web-based. With the rapid spread of the Internet in Japan, UMIN users dramatically increased.

The UMIN Center subsequently started to provide three major information services: (1) the ELBIS (Electronic Library for Biomedical Sciences) as of 1997, (2) the INDICE (Internet Data and Information Center of Clinical Research) as of 2000, and (3) the EPOC (Evaluation System of Postgraduate Clinical Training) as of 2004.

In April 2002, the UMIN Center became an independent entity, with the adjusted name of University Hospital Medical Information Network Center, as per an internal arrangement at the University of Tokyo Hospital. In 2003, a budget for a new

professor position was officially approved by the Ministry of Education, Culture, Sports, Science and Technology. Then, Dr. Kiuchi was promoted to become the first professor of the UMIN Center on April 1, 2004. The UMIN Center became part of the Faculty of Medicine, as the Department of Health Communication, School of Public Health, which was established in April 2007.

Clinical Activities

Although the UMIN Center is one of the central medical examination and treatment institutions of the University of Tokyo Hospital, the center does not provide direct patient care services, but provides services for medical researchers and practitioners throughout Japan. We currently have about 470,000 registrants, and approximately 120,000,000 monthly website accesses, which is currently in the scale of the world's highest access rates. The service extends to study / education / medical examination and treatment / hospital duties and encompasses many divergences as indicated below:

■ Research: <http://www.umin.ac.jp/research>

AC: Information for Academic Conferences
 ELBIS: Electronic Library for Biomedical Sciences
 FIND: Fund Information Database
 INDICE: Internet Data and Information Center of Clinical Research
 ROCOLS: Recruiting System for Our Colleagues' and Students'
 CTR: Clinical Trial Registry
 ICDS: Individual Case Data Sharing System

■ Education: <http://www.umin.ac.jp/education>

CC-EPOC: Clinical Clerkship E-Portfolio of Clinical Training
 PG-EPOC: E-Portfolio of Clinical Training 2
 Debut2: Dental Training Evaluation and Tabulation System
 L: E-learning system
 ARIA: Online Recruiting System for General Use

■ Medical Examination and Treatment

<http://www.umin.ac.jp/uhosp/>

- Intoxication database
- Ministry of Education, Culture, Sports, Science and Technology document public information system
- National university hospital-related medical dispute report
- Lists for people and committees
- Various government official appointments, administrative websites and ML

■ General Services

- (1) General information and search
 - Medical / biology related websites
 - Medical terminology
 - A medical research organization / medical institution database
- (2) Services for information providers
 - Web service for public
 - Web service for members
 - Website preservation service
- (3) Communication support
 - E-mail
 - Listserv
 - Discussion board
 - File exchange

Teaching Activities

Please refer to the Department of Health Communication for information about graduate and undergraduate education.

Research Activities

Please refer to the Department of Health Communication for information about research activities.

References

Please refer to the Department of Health Communication.

Department of Disaster Medical Management

Professor

Kent Doi, M.D.,Ph.D.

Assistant Professor

Hiroko Yuzawa M.D.,Ph.D

Homepage <https://www.h.u-tokyo.ac.jp/patient/depts/dmm/>

Introduction and Organization

Responding to the Great East Japan Earthquake in 2011, the University of Tokyo Hospital has decided to set out to establish “disaster medical management studies” in terms of need not only to provide medical treatment at the time of disaster but also to develop a new academic field that provides bird’s-eye view on overall disaster medicine. In March 2012, we made an announcement to establish “Department of Disaster Medical Management” in the Public Comment.

In July 2012, Associate Professor Dr. Hiroyuki Nakao was assigned the post as the first General Manager of the Department of Disaster Medical Management. Afterwards, in January 2015, Professor Dr. Tadashi Iwanaka, the Hospital Vice Director, was assigned the post as the second General Manager. In April 2015, Professor Dr. Masaomi Nangaku, the Hospital Vice Director in charge of crisis management and disaster prevention, was assigned the post as the third General Manager. In 2021, Professor Kent Doi has been assigned the post as the General Manager of the Department of Disaster Medical Management and was appointed as the chairman of the in-hospital Disaster Prevention Committee.

This department belongs to the Central Clinical Facilities Division and is involved in activities within this hospital and inside/outside of the University.

In order to establish disaster medical management studies, we are aiming at 1) fostering leaders who can develop plans for disaster medicine and educate

personnel engaged in disaster medicine, 2) relationship building with relevant institutions for establishing a system for the University of Tokyo Hospital to lead disaster medicine and 3) developing a system as a base of formation of organizations at the time of disaster.

Clinical activities

Since 2012, the Disaster Prevention Committee carries out planning and conduct the University of Tokyo Hospital Comprehensive Disaster Drill regularly. Drills of launching a new earthquake early warning system, building hospital headquarter for disaster control, reporting in-hospital damage situation, establishing triage and casualty clearing station, triage and rescue of mass casualties, were performed yearly with cooperation of the University of Tokyo, the Metropolitan Tokyo Fire Department, and the Ministry of Health Labor and Welfare.

Teaching activities

The Center provides education regarding disasters to new employees and supports disaster-related training activities in each department of the hospital. As for off-campus educational activities, the center provides support for planning disaster drills at other hospitals and gives educational lectures.

Research activities

We are seeking ways of cooperation between institutions through workshops with relevant institutions from the perspective that day-to-day cooperation with relevant institutions can be also utilized at the time of disaster. We consider that it can be also utilized for cross-business formation of organizations at the time of disaster.

References

1. Sato Y, Inokuchi R, Yamamoto M, Horie R, Asada T, Matsubara T, Doi K. Impact of renal dysfunction on the diagnosis of acute pancreatitis using urinary trypsinogen-2: A retrospective study. *Nephrology (Carlton)*. 2024 Jun;29(6):338-343.
2. Kameda S, Maeda A, Maeda S, Inoue Y, Takahashi K, Kageyama A, Doi K, Fujii T. Dose of nafamostat mesylate during continuous kidney replacement therapy in critically ill patients: a two-centre observational study. *BMC Nephrol*. 2024 Feb 26;25(1):69.
3. Ohbe H, Sasabuchi Y, Doi K, Matsui H, Yasunaga H. The authors reply. *Crit Care Med*. 2024 Feb 1;52(2):e108-e109.
4. Arashiro T, Miwa M, Nakagawa H, Takamatsu J, Oba K, Fujimi S, Kikuchi H, Iwasawa T, Kanbe F, Oyama K, Kanai M, Ogata Y, Asakura T, Asami T, Mizuno K, Sugita M, Jinta T, Nishida Y, Kato H, Atagi K, Higaki T, Nakano Y, Tsutsumi T, Doi K, Okugawa S, Ueda A, Nakamura A, Yoshida T, Shimada-Sammori K, Shimizu K, Fujita Y, Okochi Y, Tochitani K, Nakanishi A, Rinka H, Taniyama D, Yamaguchi A, Uchikura T, Matsunaga M, Aono H, Hamaguchi M, Motoda K, Nakayama S, Yamamoto K, Oka H, Tanaka K, Inoue T, Kobayashi M, Fujitani S, Tsukahara M, Takeda S, Stucky A, Suzuki T, Smith C, Hibberd M, Ariyoshi K, Fujino Y, Arima Y, Takeda S, Hashimoto S, Suzuki M. COVID-19 vaccine effectiveness against severe COVID-19 requiring oxygen therapy, invasive mechanical ventilation, and death in Japan: A multicenter case-control study (MOTIVATE study). *Vaccine*. 2024 Jan 25;42(3):677-688.
5. Hayase N, Yamamoto M, Asada T, Isshiki R, Doi K. Tachycardia and Acute Kidney Injury among Critically Ill Patients with Sepsis: A Prospective Observational Study. *Blood Purif*. 2024;53(8):641-649.
6. Pickkers P, Angus DC, Bass K, Bellomo R, van den Berg E, Bernholz J, Bestle MH, Doi K, Doig CJ, Ferrer R, Francois B, Gammelager H, Pedersen UG, Hoste E, Iversen S, Joannidis M, Kellum JA, Liu K, Meersch M, Mehta R, Millington S, Murray PT, Nichol A, Ostermann M, Pettilä V, Solling C, Winkel M, Young PJ, Zarbock A; REVIVAL investigators. Phase-3 trial of recombinant human alkaline phosphatase for patients with sepsis-associated acute kidney injury (REVIVAL). *Intensive Care Med*. 2024 Jan;50(1):68-78.

**Center for Disease Biology and
Integrative Medicine**

Laboratory of Molecular Biomedicine for Pathogenesis

Associate Professor

Satoko Arai, Ph.D.

※The following information is the same as that of the previous year for certain reasons.

Official Website <http://tmlab.m.u-tokyo.ac.jp/>

Research

Our laboratory focuses on clarification of the pathogenesis of various diseases and the related physiological machineries in cellular and molecular aspects. Based on our technical advantage in gene manipulation via gene knockout and transgenesis, we give high priorities to *in vivo* analyses. This will definitely contribute to the direct therapeutic application of our findings. Since our rationale is to challenge to uncharacterized disease mechanisms and physiologies, we will not restrict our interest, strategy or technique employed, in certain specific field. Rather, we will expand our research area by establishing different collaborations with a broad spectrum of researchers. We believe this fits to the policy of the CDBIM, which aims the development of a comprehensive science including the fundamental and clinical medicines, and the biotechnology. Overall, we will attempt to discover novel biological insights rather than to study details of previously characterized physiologies, by targeting molecules newly identified by ourselves. Now, we are focusing on the following major projects.

AIM (Apoptosis Inhibitor of Macrophage) as a master switch to various modern diseases.

The rapid change in lifestyles and eating habits in today's society are thought to be the cause of various disorders; metabolic syndrome and lifestyle-related diseases increase the risk of developing obesity, diabetes, and cardiovascular disease; a fatty liver leads

to NASH and liver disease, may result in liver cancer; autoimmune disease followed by obesity, chronic renal failure, and Alzheimer's disease are considered as well. We hypothesize that such various modern disorders, seemingly unrelated at first sight, share the common underlying pathological condition and mechanism, and the group of molecules exists as the master switch, regulating the varied conditions.

We found a soluble apoptosis inhibitor factor largely produced by tissue macrophage, named AIM (apoptosis inhibitor of macrophage). Our recent studies showed that AIM plays an important role in regulating the pathological condition of the modern diseases.

AIM is produced by macrophage and largely presents in bloodstream as a soluble molecule. Once AIM is incorporated into adipose tissue, it progression of obesity. However, when this process undergoes effectively and excessively under the obese condition, oppositely to control the progression of obesity, chronic inflammation of adipose tissue and insulin resistance are triggered and Type II diabetes and atherosclerosis are worsen.

Moreover, because AIM binds to IgM in bloodstream, it leads to production of various auto-antibodies, especially under the obese condition. This suggests that the obesity is the cause of autoimmune disease. Other studies showed that liver disease, cancer, and kidney disease worsen under low concentration of AIM. It is suggested that the concentration of AIM in bloodstream differentiates the

outcome and the risk of getting various diseases.

The project was accepted for Advanced Research and Development Programs for Medical Innovation, Leading Advanced Projects for medical innovation (LEAP) 2019 (FY2019-2023), on Japan Agency for Medical Research and Development (AMED).

Finding the mechanism on the regulation of AIM activity will shed light on developing a diagnostics and potential treatments to modern diseases. We will focus on the details of involvement of AIM to the various diseases by generating a mouse model. Also, cohort study is carried out using and analyzing the human specimen, aiming to develop a novel drug treatment.

Additionally, we worked on the project regarding the development of novel therapy against the infectious diseases based on the phagocytic mechanism, founded by Research Program on Emerging and Re-emerging Infectious Diseases (AMED FY2020-2021).

Lab Activities

We believe that the following three things are essential for research in medical biology: ideas, strategies, and experimental techniques. Therefore, the goal of our education is to let the students acquire as wide range of techniques as possible during their Master/PhD courses and to cultivate ideas and strategies for research during their postdoctoral period. In addition, since the establishment of our laboratory in 2006, we have been constructing an international research environment by regularly organizing a series of seminars by leading overseas researchers and creating as many opportunities as possible for young researchers to have discussions in English, based on the extensive friendships cultivated by Professor Miyazaki's long-term overseas research experience. In addition, we regularly hold joint meetings with universities in Japan and abroad to exchange each other's research progression and to explore the development of research through multifaceted discussions, as well as to provide opportunities for students to present and discuss their research and to interact with researchers. This year's seminars and meetings were postponed in view of the situation under the COVID-19.

Publications

1. Matsuura T, Maehara N, Hirota A, Eguchi A, Yasuda K, Taniguchi K, Nishijima A, Matsuhashi N, Shiga Y, Ishii R, Iguchi Y, Tanabe K, Arai S, & Miyazaki T. Two independent modes of kidney stone suppression achieved by AIM/CD5L and KIM-1. *Commun Biol.* 5:783 (2022).

Laboratory of Structural Physiology

Lecturer

Sho Yagishita, M.D. Ph.D.

Homepage <https://sites.google.com/view/ut-strphys>

Introduction and Organization

The Center for Disease Biology and Integrative Medicine (CDBIM) has been established in 2003, and elected Dr. Kasai as the professor of the Division of Basic Medical Sciences (2) of CDBIM in July of 2004. Dr. Kasai was in the National Institute for Physiological Sciences, and officially took office in the University of Tokyo in November, 2005. The Kasai laboratory has moved to the first building of Faculty of Medicine in January, 2006. It belongs to the Section of Functional Biology in the Graduate School of Medicine. Its name has been changed from Division of Biophysics to Laboratory of Structural Physiology in the April, 2008. Dr. Kasai has also appointed as a principal researcher in the International Research Center of Neurointelligence (IRCN), the Institute of Advanced Studies of the University of Tokyo since it has established in 2017.10, and the laboratory is cooperating the activity of IRCN. Dr. Kasai retired in March 2022.

The 10 members of our laboratories in the April of 2023 are Sho Yagishita (Lecturer), Mio Tajiri (Project Researcher), Sachio Umemoto (Project Researcher), Daria Sharapova (Project Researcher), Hidefumi Ohmi (D2), Wenying Zhong (D1), Karin Yamaguchi (M2), and as technical staffs, Masayoshi Asaumi, Akiko Abe, and Nobuko Iura.

Teaching activities

We gave two lectures of physiology for undergraduate students, was responsible for one student experiment, one lecture of physiology and

neuroscience for master course students. One undergraduate student joined the activity of our laboratory for free quarter (FQ).

Research activities

We analyze monoamine functions in the brain at multiple levels of the molecular, cellular, and system by combining several experimental techniques including two-photon excitation microscopy, molecular biology, electrophysiology, behavioral experiments and animal MRI.

Dopamine sends dense projection to the nucleus accumbens, which mainly consists of the neurons express dopamine type 1 receptors (D1 neurons) and D2 receptors (D2 neurons). When an unexpected reward is given in reward-based conditioning learning, dopamine exhibits transient increase from the steady state, which driving classical conditioning learning in which a conditioned stimulus (CS) such as sound is associated with a reward (unconditioned stimulus, US) such as water. After the conditioning, animals predict rewards from CS and elicit conditioned reflexes. Furthermore, dopamine exhibits transient decrease when the expected rewards do not come. We have previously shown that the D2 receptor detects this transient decrease in dopamine.

Since dopamine D2 receptor is a therapeutic target for schizophrenia and methamphetamine induces positive schizophrenia-like symptoms, including delusional symptoms, we conducted a study to investigate these positive symptoms using a methamphetamine-based

model. Mice were subjected to a month-long cognitive task while receiving small, non-dependence-inducing doses of methamphetamine, which inhibits transient dopamine decrease. Remarkably, when these mice were placed in a non-operational experimental task chamber, those that had previously performed the cognitive task under stimulant conditions exhibited task-like behaviors, as if perceiving a reward or cue stimulus. This phenomenon was absent in mice that had either not received stimulants or not engaged in the cognitive task. Additionally, administration of a D2 receptor blocker suppressed this behavior. Measurements of dopamine levels in the nucleus accumbens of the task-performing mice revealed dopamine release when they licked the reward port, despite the absence of an actual reward. This response was not observed in control groups. These findings led us to hypothesize that delusions may arise from pathological circuit remodeling within the striatal system. This remodeling could be driven by performing cognitive tasks that involve fluctuating dopamine levels under conditions of D2 receptor signaling dysfunction, causing dopamine to respond to stimuli that are not actually present.

References

1. Shikano Y, Yagishita S, Tanaka KF, Takata N. Slow-rising and fast-falling dopaminergic dynamics jointly adjust negative prediction error in the ventral striatum. *Eur J Neurosci.* 2023 Dec;58(12): 4502-4522. doi: 10.1111/ejn.15945. Epub 2023 Mar 10. PMID: 36843200.
2. Kasai K, Kumagaya SI, Takahashi Y, Sawai Y, Uno A, Kumakura Y, Yamagishi M, Kanehara A, Morita K, Tada M, Satomura Y, Okada N, Koike S, Yagishita S. "World-Informed" Neuroscience for Diversity and Inclusion: An Organizational Change in Cognitive Sciences. *Clin EEG Neurosci.* 2023 Nov; 54(6): 560-566. doi: 10.1177/15500594221105755. Epub 2022 Jun 12. PMID: 35695218.
3. Abe Y, Yagishita S, Sano H, Sugiura Y, Dantsuji M, Suzuki T, Mochizuki A, Yoshimaru D, Hata J, Matsumoto M, Taira S, Takeuchi H, Okano H, Ohno N, Suematsu M, Inoue T, Nambu A, Watanabe M, Tanaka KF. Shared GABA transmission pathology in dopamine agonist- and antagonist-induced dyskinesia. *Cell Rep Med.* 2023 Oct 17;4(10):101208. doi: 10.1016/j.xcrm.2023.101208. Epub 2023 Sep 28. PMID: 37774703; PMCID: PMC10591040.
4. Yawata Y, Shikano Y, Ogasawara J, Makino K, Kashima T, Ihara K, Yoshimoto A, Morikawa S, Yagishita S, Tanaka KF, Ikegaya Y. Mesolimbic dopamine release precedes actively sought aversive stimuli in mice. *Nat Commun.* 2023 Apr 27;14(1):2433. doi: 10.1038/s41467-023-38130-3. PMID: 37106002; PMCID: PMC10140067.
5. Yagishita S. Cellular bases for reward-related dopamine actions. *Neurosci Res.* 2023 Mar;188:1-9. doi: 10.1016/j.neures.2022.12.003. Epub 2022 Dec 7. PMID: 36496085.

Laboratory of Biomedical Equipment and Biomaterials

Professor

Kanako Harada, Ph.D.

Homepage <http://www.cdbim.m.u-tokyo.ac.jp/>

Introduction and Organization

The laboratory was established as one of the research divisions of the Center for Disease Biology and Integrative Medicine, which was launched on April 1, 2003. The center was a new organization that is the first of its kind to bring together the Graduate School of Medicine and the Graduate School of Engineering, and this laboratory is working to pioneer a new medicine and engineering collaboration from the engineering side, approaching basic medicine and clinical medicine. In 2016, the laboratory relocated to the 8th floor of the Clinical Research Building A.

Educational activities

Professor Harada teaches courses related to biomedical engineering at the Graduate School of Medicine, including Medical Science Common Lecture IV and Medical Materials and Mechanical Engineering. In the Graduate School of Engineering, she teaches Bioengineering Exercise for Social Implementation 1 and 2, Engineering Competency III - Summer Camp -, Engineering Competency I - PBL -, Overview of mechano bioengineering, and Clinical Biomechanics. She has a system in place to guide students to actively present their research at academic conferences and publish papers. She also welcomes visits to her laboratory by junior high school and high school students.

Research activities

Our research and development efforts are focused on the field of medical devices, with a particular

emphasis on mechanical engineering. Our research encompasses the following areas: surgical skill assessment, surgical robots, and robotics for scientific discovery.

1. Surgical Skill Assessment

Our research involves data analysis with the objective of quantifying surgical skills. We have developed artificial intelligence (AI) capable of processing microscopic images, and we have developed a method for estimating the pose of a needle for microsurgery.

2. Surgical Robots

We are conducting research on surgical robots for use in pediatric surgery, neurosurgery, ophthalmology, etc. In particular, we are developing robotic control for automatic anastomosis in confined spaces. We have developed a robot that automates the looping task using a simulator. Besides, a robot that automates membrane peeling in the fundus of the eye has been developed.

3. Robots for Scientific Discovery

Our research and development endeavors are focused on leveraging robotics to facilitate the manipulation of model organisms, such as mice. We have developed robotic platforms that enable precise manipulation, and its remote control from Stockholm to Tokyo was successfully demonstrated. In addition,

we have developed a 3D camera capable of constructing the three-dimensional shape of a fine object. This camera has been successfully utilized to automate robotic manipulation by detecting small changes in the object.

References

- (1) Murilo Marques Marinho, Juan José Quiroz Omaña, Kanako Harada, "A Multiarm Robotic Platform for Scientific Exploration: Its Design, Digital Twins, and Validation," *IEEE Robotics & Automation Magazine* 31(4): 10-20, 2024. DOI: 10.1109/MRA.2023.3336472
- (2) Hung-Ching Lin, Murilo Marques Marinho, Kanako Harada, "Autonomous Camera Positioning Using Vector Field Inequality Constraints" 2023 IEEE/RSJ International Conference on Intelligent Robots and Systems (IROS2023), Detroit, MI, USA, 2023 (Late Breaking Results Poster)
- (3) Enduo Zhao, Murilo Marques Marinho, Kanako Harada, "Autonomous Robotic Drilling System for Mice Cranial Window Creation: An Evaluation with an Egg Model", Accepted to 2023 IEEE/RSJ International Conference on Intelligent Robots and Systems (IROS2023), Detroit, MI, USA, 2023, pp. 4592-4599, doi: 10.1109/IROS55552.2023.10341693. **[IROS Best Application Paper Award sponsored by ICROS]**
- (4) Yuki Koyama, Murilo Marques Marinho, Kanako Harada, "Vitreoretinal Surgical Robotic System with Autonomous Orbital Manipulation Using Vector-Field Inequalities", 2023 IEEE International Conference on Robotics and Automation (ICRA2023), London, United Kingdom, May 29-June 2, 2023. (Poster presentation)
- (5) Juan Jose Quiroz Omana, Murilo Marques Marinho, Kanako Harada, "Digital Twin of a Multi-Arm Robot Platform based on Isaac Sim for Synthetic Data Generation", Workshop on Pretraining 4 Robotics 2023 IEEE International Conference on Robotics and Automation (ICRA2023) ,London, United Kingdom, May 29- June 2, 2023. (Lightning talk)

Laboratory of Clinical Biotechnology

Professor

Yuichi Tei/ Ung-il Chung, M.D.,Ph.D.

Associate Professor

Hironori Hojo, Ph.D

Assistant Professor

Hiroyuki Okada, M.D., Ph.D

※The following information is the same as that of the previous year for certain reasons.

Homepage <https://grn.tokyo/med/en/>

Introduction and Organization

The Laboratory of Clinical Biotechnology at the Center for Disease Biology and Integrative Medicine (CDBIM) was launched in April 2003 under the direction of Professor Kazunori Kataoka. As this Laboratory is expected to serve as a bridge at The University of Tokyo (UTokyo) for medical bioengineering, where medicine and engineering are closely intertwined with each other, we are conducting research on medical bioengineering through on-campus collaborations with the Graduate School of Engineering, the Graduate School of Medicine, and The University of Tokyo Hospital and its affiliated divisions such as the Division of Tissue Engineering and the Cooperative Unit of Medicine and Engineering Research. We also aim to recruit and train professionals—including physicians, dentists, pharmacists, veterinarians, life science researchers, engineering researchers, and engineers—who are equipped with a deep understanding of medical bioengineering. To achieve this, we have utilized undergraduate and graduate education programs such as the Graduate Program for Leaders in Life Innovation (GPLLI) of UTokyo.

Professor Kataoka, who directed the laboratory until March 2016, worked on the development and

clinical applications of nanotechnology-based drug delivery systems and imaging.

Professor Yuichi Tei (Ung-il Chung) has served as Director of the Laboratory of Clinical Biotechnology since November 2016. With a particular focus on skeletal tissues (bones and cartilage), we are currently studying molecular mechanisms underlying cell fate specification as well as signaling factor-based systems to manipulate cell differentiation and proliferation. We are also working on the development of novel biomaterials that will fulfill the characteristics required for *in vivo* use as scaffolds. By integrating these studies, we aim to develop novel systems for skeletal tissue engineering and regenerative medicine, in which cell differentiation and proliferation are regulated directly and locally *in situ*.

Professor Tei has a cross-appointment with the Department of Bioengineering, Graduate School of Engineering, and he also serves as Research Leader of The University of Tokyo Center for Innovation (COI) Self-Managing Healthy Society. In collaboration with the program, we are also working on the establishment of an Open Innovation Platform and the promotion of industry-academia collaborations for the social implementation of research products.

Education

The development of advanced medical systems, such as regenerative medicine and medical devices, is an important and globally growing research field in which medical biology and engineering are integrated and play important roles. Since the medicine-engineering cooperation that has occurred to date has been mainly research collaborations, the development of theoretical systems as well as education systems for the integrated field have been delayed. This often causes a mismatch between clinical needs and technological seeds. The delay is likely due to difficulties in identifying basic principles that underlie both of the quite different fields of medical biology and engineering, when they are integrated.

Through multi-discipline and cross-sectional research projects integrating medical biology and engineering, we aim to train biomedical professionals who themselves integrate medicine and engineering; that is, engineers who understand medical needs and medical researchers who understand technological seeds. We are offering students with varying backgrounds opportunities to study a broad spectrum of biomedical engineering—from basic principles of living organisms to advanced medical systems—on the basis of each student's expertise. We also collaborate with The University of Tokyo COI Self-Managing Healthy Society, in order to utilize the Open Innovation Platform in which all stakeholders from industry, government, academia, and the private sector join the program as equals from the start, as a practical education tool for developing the aforementioned biomedical professionals.

Research

We pursue two scientific interests with a particular focus on skeletal tissues (bones and cartilage): (1) the manipulation of progenitor cell differentiation and proliferation based on the understanding of molecular mechanisms underlying cell fate specification, and (2) the development of novel biomaterials fulfilling the characteristics required for *in vivo* use as scaffolds. We aim to develop novel systems for skeletal tissue engineering and regenerative medicine in which cell differentiation and proliferation are directly regulated *in situ*. The following four projects are ongoing.

1. Understanding of epigenome dynamics and gene regulatory networks during cell fate specification processes

Organogenesis depends on cell fate specification and the subsequent differentiation and maturation of specified cells. Gene transcription underlies a series of processes; appropriate genes are transcribed with appropriate amounts and at the appropriate timing for inducing cell activities and characteristics. In this context, the epigenome works as a main switch for gene expression. Transcription factors, which bind to the genome in a sequence-dependent manner, in turn increase the amount of transcripts, in a manner that is analogous to turning up the volume of a radio.

Against this background, we seek to understand the mechanisms of cell fate specification, cell differentiation, and cell maturation during skeletal development with a particular focus on epigenome dynamics and genomic targets of transcription factors. We also plan to apply the knowledge gained to the development of regenerative therapies for skeletal tissue defects. Here we rely on the following approaches: (1) observations of intracellular events by direct and comprehensive techniques, (2) the construction of hypotheses driven by these observations, and (3) verification of the hypotheses. Thus, the approach starts with the collection of genome-scale data on gene expression, epigenome, and transcription factor binding sites by taking advantage of next-generation sequencers. The data are analyzed by bioinformatics approaches, leading to the construction of a new biological hypothesis. Each hypothesis is verified by molecular-biological approaches and mouse genetics. With this research strategy, we are investigating the regulatory landscape on the genome that determines the specification of bone- and cartilage-forming cells, osteoblasts and chondrocytes, respectively, and their phenotypes. A series of studies reveals transcriptional networks that mediate pluripotency and the differentiation of pluripotent stem cells (*Stem Cells* 31:2667, 2013), epigenome dynamics and modes of action of master transcription factors that specify osteoblasts and chondrocytes, and the gene regulatory networks mediated by those master transcription factors (*Cell Reports* 12:229, 2015; *Developmental Cell* 37:238, 2016; *Development* 143:3012, 2016; *Trends in Genetics* 32:774, 2016;

Regen Ther 6, 100-107, 2017; *Int J Mol Sci.* 20(24). pii: E6324, 2019; *Bone.* 137:115458, 2020; *Nat Commun.* 12(1):6271, 2021; *Cell Rep* 40(10), 2022; *Nat Commun.* 13(1):6187, 2022; *Nat Commun.* 13(1):2654, 2022). A fuller understanding of cell fate specification processes during skeletal formation, we believe, will enable the development of novel therapeutic strategies, in which bone and cartilage repair and regeneration are induced by the manipulation of the specification processes.

2. The development of tissue-development modeling systems using pluripotent stem cells

It would be ideal to study the mechanisms of tissue formation and maintenance in *in vivo* working cells. However, the number of cells that can be obtained *in vivo* is often not sufficient for molecular-level mechanistic studies; this is a technical limitation in studying skeletal development and regeneration. Pluripotent stem cells (PSCs; i.e., embryonic stem cells—ES cells and induced pluripotent stem cells—iPS cells), which have the ability to self-renew and differentiate into all of the lineages present in the body, are a promising tool for study; reproducing organogenesis and metabolism *in vitro* potentially overcomes the above limitation. Considering the safety, cost, and biological conciseness, it would be better to induce tissues from PSCs under defined conditions by using small molecules while avoiding differentiation into lineages of no interest.

We have therefore been developing protocols for directing mouse and human PSCs toward osteoblasts under defined conditions using only small molecules, while recapitulating *in vivo* osteoblast development (*Stem Cell Reports* 2:751, 2014). With the protocol, we addressed a molecular mechanism in osteoblast development (*Stem Cell Reports.* 15(1):125-139, 2020). We are also attempting to apply the protocols to the generation of PSC-derived bone-like tissues, in which distinct cell populations regulating bone formation and maintenance (osteoblasts, osteocytes, and osteoclasts) function three-dimensionally on culture dishes (*Science Advances* 3:e1602875, 2017). Such culture systems in combination with human PSCs could enable us to reproduce human bone development and metabolism in a physiologically relevant manner. These systems will also allow us to

visualize bone metabolism *in vitro* with imaging techniques, contributing to drug discoveries for the treatment of various bone diseases such as osteoporosis, and to our understanding of the diseases' pathophysiology and of the molecular mechanisms underlying skeletal formation and maintenance.

3. The identification of bioactive factors that induce bone/cartilage formation and their application to bone/cartilage repair

Skeletal formation is regulated by various signaling pathways and transcription factors. The manipulation of key pathways and/or factors would enable us to not only induce skeletal formation and regeneration, but also suppress the progression of skeletal degeneration. Thus, we are carrying out molecular-biological and mouse genetic studies to elucidate the roles of osteogenic and chondrogenic signaling pathways as well as the modes of their actions. Based on these basic findings, we are also working on the identification and application of bioactive molecules that induce osteogenesis and chondrogenesis.

We have been focusing on: (1) hedgehog (Hh) signaling-mediated cell fate specification during osteoblast development (*Development* 131:1309, 2004; *Journal of Biological Chemistry* 282:17860, 2012; *Journal of Biological Chemistry* 288:9924, 2013), and (2) transcriptional regulation mediating osteoblast differentiation and maturation (*Developmental Cell* 14:689, 2008; *PLOS ONE*, 2014). These studies further extend to the development of the small molecule-based treatment of bone fractures, using the Hh signaling-activator molecule SAG (*Biochemical and Biophysical Research Communications* 479:772, 2016) and bone regenerative therapy with SAG-loaded calcium phosphate artificial bones (*Biomaterials* 34:5530, 2013). By combining biological findings with engineering techniques, we are working on bone regeneration by plasmid delivery using polymeric nanomicelles as nucleic acid carriers (*Molecular Therapy* 15:1655, 2007) and the suppressive treatment of cartilage degeneration by mRNA delivery (*Scientific Reports* 6:18743, 2016).

We have also identified novel small molecules that induce bone and cartilage formation (*Biochemical and Biophysical Research Communications* 357:854, 2007; *Annals of Rheumatic Diseases* 72:748, 2013),

through the screening of compound libraries with cell-based sensors enabling the high-throughput detection of osteoblast and chondrocyte differentiation (*Biochemical and Biophysical Research Communications* 376:375, 2008; *Journal of Bone and Mineral Metabolism* 28:627, 2010).

4. The development of tissue-inductive implant devices integrating tissue-regeneration signals and highly functional and biocompatible biomaterials

In the current aging society, the treatment of tissue defects in locomotive organs is a crucial task to achieve the extension of healthy life expectancy. There is an urgent need for low-invasive reconstruction therapies that recover lost or damaged tissues with the same functional and aesthetic qualities as those in healthy states. The transplantation of donor tissues obtained from patients' healthy sites has been widely used for tissue reconstruction (autologous transplantation). However, this strategy often causes post-operative pain and the cosmetic disturbance of donor sites. Although reconstruction with biomaterials avoids donor site problems, its tissue induction capacity is generally inferior to that of autologous transplantation.

As signaling networks mediating the formation and regeneration of tissue and organs are being elucidated by recent advances in stem cell biology, some biomaterial-based systems are being developed for delivering signaling factors to target tissues. We are studying these approaches as mentioned above. In addition, the emergence of three-dimensional (3D) printers has rapidly improved the techniques available for controlling the shapes of scaffold materials. By controlling the 3D shape of biomaterials, we have been attempting to improve the performance of biomaterials for tissue repair. We developed custom-made calcium phosphate artificial bone (CT-bone) that is manufactured using 3D printers and have applied them to clinical settings in cooperation with the Department of Oral and Maxillofacial Surgery, The University of Tokyo Hospital (*Journal of Artificial Organs* 9:234, 2006; *Journal of Artificial Organs* 12:200, 2009; *Regenerative Therapy* 5:1, 2016). We have also worked on the development and application of tetrapod-shaped calcium phosphate artificial bone (Tetrabone), which is fabricated at 1-mm size by

injection molding, and a custom-made titanium mesh cage fabricated by laser sintering (*Acta Biomaterialia* 8:2340, 2012; *Biomaterials* 35:3229, 2014).

However, either signaling factors or biomaterials alone are not sufficient for the clinically sufficient regeneration of tissues, and interface units integrating them are necessary for fully utilizing their performance. A candidate for the integrating interface unit is a high-performance hydrogel unit, which maintains the spatial arrangement of signaling factors and can deliver them to target cells at a selected timing by temporally controlled degradation. However, conventional hydrogels do not provide the characteristics required for an integrating interface unit.

In cooperation with Professor Takamasa Sakai at the Department of Bioengineering, UTokyo, we are developing a high-performance hydrogel unit that fulfills the necessary characteristics, based on knowledge and techniques that we have accumulated regarding the design and fabrication of novel hydrogels (*Macromolecules* 41:5379, 2008; *Science* 343:873, 2014; *Advanced Materials* 27:7407, 2015; *Nature Biomedical Engineering* 1:44, 2017; *Phys Rev Lett.* 125(26):267801, 2020; *RSC Advances* 11, 23637, 2021). The high-performance hydrogel unit would integrate signaling factors with shape-controlled scaffold materials, leading to the development of implant devices that work as scaffolds for tissue repair and also as carriers of bioactive factors. Through a series of these studies, we are aiming to create a "four-dimensional scaffold system" that achieves efficient tissue regeneration by controlling cell proliferation and differentiation in temporal and spatial manners. The system will not only be applicable to the regeneration of other tissues; it will also contribute to the development of basic technologies for the temporal-spatial control of *in situ* tissue formation, which is versatile in the prevention, diagnosis, and treatment of various diseases.

Publications

1. Kitaura Y, Nakamura U, Awada C, Yamaguchi M, Kim M, Ikeda Y, Matsuo Y, Moriishi T, Sawase T, Chung UI, Hojo H*, Ohba S*. Orally administrable peptides derived from egg yolk promote skeletal repair and ameliorate

- degenerative skeletal disorders in mouse models. *Regen Ther* 21:584-595, 2022
2. Nagata K, Hojo H, Chang SH, Okada H, Yano F, Chijimatsu R, Omata Y, Mori D, Makii Y, Kawata M, Kaneko T, Iwanaga Y, Nakamoto H, Maenohara Y, Tachibana N, Ishikura H, Higuchi J, Taniguchi Y, Ohba S, Chung UI, Tanaka S, Saito T*. Runx2 and Runx3 differentially regulate articular chondrocytes during surgically induced osteoarthritis development. *Nat Commun*. 13(1): 6187, 2022.
 3. Iwahashi S, Lyu J, Tokumura K, Osumi R, Hiraiwa M, Kubo T, Horie T, Demura S, Kawakami N, Saito T, Park G, Fukasawa K, Iezaki T, Suzuki A, Tomizawa A, Ochi H, Hojo H, Ohba S, Hinoi E*. Conditional inactivation of the L-type amino acid transporter LAT1 in chondrocytes models idiopathic scoliosis in mice *J Cell Physiol*. 2022 Sep 26. doi: 10.1002/jcp.30883.
 4. Hojo H*, Saito T, He X, Guo Q, Onodera S, Azuma T, Koebis M, Nakao K, Aiba A, Seki M, Suzuki Y, Okada H, Tanaka S, Chung UI, McMahon AP, Ohba S*. Runx2 regulates chromatin accessibility to direct the osteoblast program at neonatal stages. *Cell Reports*. 40(10), 2022
 5. Hojo H, Ohba S*. Sp7 Action in the Skeleton: Its Mode of Action, Functions, and Relevance to Skeletal Diseases. *Int J Mol Sci* 23(10):5647, 2022
 6. Nakayama M, Okada H, Seki M, Suzuki Y, Chung UI, Ohba S, Hojo H*. Single-cell RNA sequencing unravels heterogeneity of skeletal progenitors and cell-cell interactions underlying the bone repair process. *Regen Ther*. 21:9-18, 2022
 7. Doi T*, Hojo H, Ohba S, Obayashi K, Endo M, Ishizaki T, Katoh A, Kouji H. Involvement of activator protein-1 family members in β -catenin and p300 association on the genome of PANC-1 cells. *Heliyon*. 8(2):e08890, 2022
 8. Katashima T*, Kobayashi R, Ishikawa S, Naito M, Miyata K, Chung UI, Sakai T. Decoupling between Translational Diffusion and Viscoelasticity in Transient Networks with Controlled Network Connectivity. *Gels*. 8(12): 830, 2022.
 9. Saito Y*, Nakamura S, Tanaka A, Watanabe R, Narimatsu H, Chung UI. Evaluation of the validity and reliability of the 10-meter walk test using a smartphone application among Japanese older adults. *Front Sports Act Living*. 4:904924, 2022.
 10. Ishikawa S, Yoshikawa Y, Kamata H*, Chung UI, Sakai T*. Simple Preparation of Injectable Hydrogels with Phase-Separated Structures That Can Encapsulate Live Cells. *ACS Appl Mater Interfaces*. 14(31):35444-35453, 2022.
 11. Saito Y*, Nakamura S, Tanaka A, Watanabe R, Narimatsu H, Chung UI. Checking the validity and reliability of the Japanese version of the Mini-Cog using a smartphone application. *BMC Res Notes*. 15(1):222, 2022.
 12. Katashima T*, Kudo R, Naito M, Nagatoishi S, Miyata K, Chung UI, Tsumoto K, Sakai T*. Experimental Comparison of Bond Lifetime and Viscoelastic Relaxation in Transient Networks with Well-Controlled Structures. *ACS Macro Lett*. 11(6):753-759, 2022.
 13. Pham H, Svensson T*, Chung UI, Svensson AK. Sleep Satisfaction May Modify the Association between Metabolic Syndrome and BMI, Respectively, and Occupational Stress in Japanese Office Workers. *Int J Environ Res Public Health*. 19(9):5095, 2022.
 14. Omatsu Y, Aiba S, Maeta T, Higaki K, Aoki K, Watanabe H, Kondoh G, Nishimura R, Takeda S, Chung UI, Nagasawa T*. Runx1 and Runx2 inhibit fibrotic conversion of cellular niches for hematopoietic stem cells. *Nat Commun*. 13(1): 2654, 2022.
 15. Fujiyabu T, Sakumichi N, Katashima T, Liu C, Mayumi K, Chung UI, Sakai T*. Tri-branched gels: Rubbery materials with the lowest branching factor approach the ideal elastic limit. *Sci Adv*. 8(14):eabk0010, 2022.
 16. Matsubara T, Soma K, Yamada I, Fujita H, Yoshitani J, Oka H, Okada H, Tanaka S*. Offset nail fixation for intertrochanteric fractures improves reduction and lag screw position. *PLoS One*. 17(11):e0276903, 2022.
 17. Tachibana N, Chijimatsu R, Okada H, Oichi T, Taniguchi Y, Maenohara Y, Miyahara J, Ishikura

H, Iwanaga Y, Arino Y, Nagata K, Nakamoto H, Kato S, Doi T, Matsubayashi Y, Oshima Y, Terashima A, Omata Y, Yano F, Maeda S, Ikegawa S, Seki M, Suzuki Y, Tanaka S, Saito T*. RSPO2 defines a distinct undifferentiated progenitor in the tendon/ligament and suppresses ectopic ossification. *Sci Adv*. 8(33):eabn2138, 2022

18. Omata Y, Okada H, Uebe S, Izawa N, Ekici AB, Sarter K, Saito T, Schett G, Tanaka S*, Zaiss MM. Interspecies Single-Cell RNA-Seq Analysis Reveals the Novel Trajectory of Osteoclast Differentiation and Therapeutic Targets. *JBMR Plus*. 6(7):e10631, 2022.

Laboratory of Microenvironmental and Metabolic Health Sciences

Professor

Makoto Murakami, Ph.D. (also engaged in Department of Physiological Chemistry and Metabolism)

Associate Professor

Seiichiroh Ohsako, Ph.D., D.V.M.

Assistant Professor

Yoshitaka Taketomi, Ph.D.

Research Assistant

Hiroyasu Sato, Ph.D.

Research Assistant

Yuki Nagasaki, Ph.D. (engaged in Department of Physiological Chemistry and Metabolism)

Home Page <http://lmmhs.m.u-tokyo.ac.jp>

Introduction

Laboratory of Environmental Health Sciences of the Center for Disease Biology and Integrative Medicine moved the laboratory from the 3rd floor of the Medical Faculty of Medicine Building 1 to the 8th floor of the Clinical Research Center A on October 2016 and modified the laboratory name to Laboratory of Microenvironmental and Metabolic Health Sciences on April 2017, aiming at examining biochemistry and microenvironmental biology of lipids as well as environmental toxicology. One professor, one associate professor, one assistant professor, one research assistant, two project researchers, two visiting researchers, four graduate students (doctoral course), three external researchers from clinical teams, and four undergraduate students conducted the research in 2024. Since July 2024, Murakami has also been a professor in the Department of Physiological Chemistry and Metabolism, and Nagasaki has been assigned to this department as an assistant professor since August 2024.

Research activities

Laboratory of Microenvironmental and Metabolic Health Sciences was constituted by two major research projects; “lipid biology” by a group of Murakami (professor) and “environmental toxicology” by a group of Ohsako (associate professor).

1. Lipid biology (Murakami’s group)

The main theme of this research project is to clarify the role of lipids in health and diseases. Lipids supply the largest source of energy in living organisms, are main components of cell membranes, act as signal molecules, and constitute a barrier covering the body surface (four major functions of lipids). Lipids are environmental nutritional factors ingested from foods, as well as tissue microenvironmental regulators that spatiotemporally coordinate various biological responses after being metabolized to specific bioactive lipids. By performing comprehensive lipid analysis (lipidomics) on gene-manipulated mice for lipid-

metabolizing enzymes, particularly those in the phospholipase A₂ (PLA₂) family, we aim to elucidate the molecular pathophysiology of diseases (*e.g.* metabolic and immune diseases) that are problematic in modern society. Based on this, we will promote the research of Quality of Lipids (QOL) for Quality of Life (QOL) and aim at building a theoretical foundation for diagnosis, prevention and treatment of diseases involving alteration of lipid metabolism.

1) Metabolic diseases

We aim to understand the whole picture of metabolic regulation by the extracellular sPLA₂ family. sPLA₂-V (PLA2G5), secreted from hypertrophic white adipocytes in obesity, hydrolyzes phosphatidylcholine (PC) in LDL to release oleic and linoleic acids, which attenuate M1 polarization of macrophages and thereby protect from diet-induced obesity, adipose tissue inflammation, and insulin resistance (Sato et al, *Cell Metab*, 2014). sPLA₂-IID (PLA2G2D), secreted from M2-like macrophages in white adipose tissue, releases ω 3 polyunsaturated fatty acids (PUFAs) to promote cold-induced adipocyte browning and thermogenesis (Sato et al, *Cell Rep*, 2020). sPLA₂-IIE (PLA2G2E) is highly induced in brown and beige adipocytes in response to cold and its adipocyte-specific deletion leads to impairment of adipocyte browning and thermogenesis (in preparation). sPLA₂-III (PLA2G3) is preferentially expressed in the skin and colon, and its deletion in the skin leads to skin barrier dysfunction, which ultimately increases systemic type 2 immunity that counters obesity (in preparation). In addition, preliminary results indicate that sPLA₂-IIF (PLA2G2F) is expressed in pancreatic islets and that its β cell-specific deletion results in metabolic dysfunction.

Choline supplies methyl groups for regeneration of methionine and the universal methyl donor *S*-adenosylmethionine (SAM) in the liver. In mice deficient in PNPLA7 (lysophospholipase) or PNPLA8 (phospholipase A_{1/2}), both of which belong to the iPLA₂ family, endogenous choline cannot be released from membrane PC via lysophosphatidylcholine (LPC) and glycerophosphocholine (GPC), thereby preventing the transfer of choline methyl groups to methionine. This disrupts the metabolic flux of methyl groups through the methionine cycle resulting in phenotypes reminiscent of methionine insufficiency, such as poor growth, liver degeneration, muscle weakness, WAT

loss and browning, and short lifespan (Hirabayashi et al, *Cell Rep*, 2023). Skeletal muscle-specific PNPLA7-deficient mice exhibit a sarcopenia-like muscle dysfunction with mitochondrial degeneration over 6 months (submitted). In addition, mice deficient in PLAAT1 are protected from development of fatty liver, while mice deficient in PLAAT3 (also called PLA2G16) develop lipodystrophy with exaggerated fatty liver (Rahman et al, *FASEB J* 2024).

2) Skin diseases

sPLA₂-IIF, expressed in epidermal keratinocytes, produces lysoplasmalogen, a unique lysophospholipid that exaggerates psoriasis and skin cancer (Yamamoto et al, *J Exp Med*, 2015). PNPLA1, whose mutations in humans are linked to autosomal recessive congenital ichthyosis, acts as a unique transacylase to produce ω -*O*-acylceramide, an essential lipid component for the skin barrier (Hirabayashi et al, *Nat Commun*, 2017). cPLA₂ ϵ (PLA2G4E), a unique *N*-acyltransferase, transfers a fatty acid from the *sn*-1 position of PC to the amino group of phosphatidylethanolamine (PE) to yield *N*-acyl-PE (NAPE), a precursor of the anti-inflammatory lipid *N*-acylethanolamine (NAE), and counteracts psoriatic inflammation (Liang et al, *FASEB J* 2022). Deficiency of cPLA₂ δ (PLA2G4D), which has PLA₁ activity, exacerbates psoriasis, while that of cPLA₂ ζ (PLA2G4F), which has PLA₂ activity with no *sn*-2 fatty acid selectivity, delays skin wound healing (in preparation). Epidermal sPLA₂-III is coupled with the production of prostaglandins (PGE₂, PGF_{2 α}), and skin-specific loss of sPLA₂-III, as well as that of PGE₂ and PGF_{2 α} receptors (EP4, FP), results in impaired skin barrier function, enhanced type 2 immunity, increased scratching behavior, and disturbed skin microbiota. These atopic dermatitis-like symptoms are further associated with bronchial asthma, reminiscent of allergic march (in preparation). In addition, mice deficient in ABHD12B, whose expression is markedly reduced in patients with scleroderma, have reduced levels of unique ceramide metabolites and display exacerbated skin fibrosis (in preparation).

3) Immunological diseases

sPLA₂-III secreted from mast cells integrates mast cell maturation by mobilizing LPA from extracellular vesicles and coordinately inducing integrins, IL-33, autotaxin (ATX), and PGD₂ via LPA₁ receptor on

stromal fibroblasts (Taketomi et al, *Nat Immunol* 2013; Taketomi et al, *Immunity* 2024). PAF-AH2, a unique PLA₂ that hydrolyzes oxidized phospholipids, ensures optimal mast cell activation and thereby allergic reaction by producing unique EPA/DHA metabolites (ω 3 epoxides) (Shimanaka et al, *Nat Med* 2017). sPLA₂-XIIIA (PLA2G12A), secreted from stromal fibroblasts, augments mast cell activation likely through producing lysophospholipids (in preparation). LPA produced by sPLA₂-III in the airway epithelium suppresses asthma via LPA₂ receptor (Hamu-Tanoue et al, *FASEB J* 2024). sPLA₂-III secreted from eosinophils promotes eosinophil infiltration by mobilizing LPA from membrane phospholipids in dying cells (in preparation). In sepsis, sPLA₂-V degrades damaged erythrocyte membranes to promote hemolysis (in preparation). sPLA₂-XIIIA is induced in activated CD4⁺ T cells and involved in Th17 differentiation. Global or T cell-specific sPLA₂-XIIIA-deficient mice have fewer Th17 and $\gamma\delta$ T cells, thereby attenuating Th17-driven disease models such as psoriasis and arthritis. sPLA₂-XIIIA mobilizes LPE and LPA from extracellular vesicles, of which LPE acts as a ligand for ROR γ t, a master transcription factor of Th17 cells (Endo et al, *Sci Immunol* 2023), and LPA augments Th17 induction mainly via LPA₂ receptor (submitted).

4) Gut microbiota

sPLA₂-IIA (PLA2G2A) in the small intestine is involved in skin pathology secondary to shaping of the gut microbiota through antimicrobial activity (Miki et al, *JCI Insight* 2022). PLA2G10 (sPLA₂-X) in the large intestine shapes the gut microbiota by releasing ω 3 PUFAs, which secondarily affect systemic metabolism (Sato et al, *Cell Rep* 2024).

5) Cancer

In B-cell lymphoma, sPLA₂-X induced in tumor-associated macrophages hydrolyzes phospholipids in tumor-derived extracellular vesicles, giving rise to sPLA₂-X-modified EVs rich in lipid mediators such as LPA and RvD2. The sPLA₂-X-modified EVs are taken up by macrophages and transmit immunosuppressive lipid signals, thereby creating a tumor-promoting tissue microenvironment (Kudo et al, *Cell Metab* 2022). sPLA₂-IID, whose expression correlates with that of immune checkpoint markers in various cancers, reduces the functions of CD8⁺ T cells and macrophages, thereby exacerbating cancer (submitted).

6) Neuronal and retinal diseases

Mutations in the human *PNPLA6* gene cause neuronal and retinal degeneration such as hereditary spastic paraplegia (SPG) and amyotrophic lateral sclerosis (ALS). PNPLA6 acts as a phospholipase B (PLA₁/A₂ + lysophospholipase), hydrolyzing PC to give rise to two fatty acids and GPC. Simultaneous deletion of PNPLA6 and its closest homolog PNPLA7 in the central nervous system, particularly in astrocytes, leads to severe neurodegenerative disorders with muscle atrophy, reminiscent of SPG and ALS (in preparation). Retina-specific deletion of PNPLA6 results in retinal degeneration, which is rescued by eyedrops of choline, a PC degradation product (Ono et al, *Nat Commun* in press). Disease-related PNPLA8 mutations prevent the proper development of cerebral organoids from human iPS cells (Nakamura et al, *Brain* 2024). PLA2G2E is induced in neurons after cerebral infarction and involved in protection against neuronal damage by mobilizing the unique lipid metabolite 15-HETrE (Nakamura et al, *Neuron*, 2023). sPLA₂-IIF is induced in the hippocampus during aging and delays the onset of dementia (submitted).

2. Environmental Toxicology (Ohsako's group)

PFOA, a type of flame-retardant fluorine-containing compound, has been reported epidemiologically as a risk factor for carcinogenesis and ulcerative colitis. PFOA production is prohibited in Europe, but in Japan the production is still going on and environmental contamination especially in tap water has become a social issue. Ahr has been reported to regulate differentiation of the helper T-cells such as Th17/Treg through binding to its endogenous ligands which are produced by intestinal bacteria. Ohsako discovered that chronic inflammatory bowel disease (IBD) accompanied by Th17 proliferation occurred while raising AhrKO mice in the SPF animal facility at Tokyo University of Science. Metagenomic analysis of the colon contents revealed the presence of a bacterial flora specific to the SPF facility at Tokyo University of Science. Based on these findings, it was concluded that the Tokyo University of Science bacterial flora is related to the onset of IBD via Ahr. Therefore, PFOA was administered to mice raised at Tokyo University of Science to examine whether there were any changes in the inflammatory response and intestinal flora. As a

result, PFOA induced IL-1 β , TGF- β , and IFN- γ , and the response was specific to the wild type. In addition, PFOA was found to increase the *Turicibacter* genus to approximately 10% of the total flora, regardless of genotype.

Teaching activities

The Laboratory of Microenvironmental and Metabolic Health Sciences/ the Department of Physiological Chemistry and Metabolism has important missions to train postdoctoral fellows to become promising scientist leaders in the field of medical sciences and environmental toxicology and to provide biochemistry, molecular biology, toxicology and environmental health courses for graduate and undergraduate students. The following lectures have been provided to students.

Graduate education

Lectures, Seminars, and laboratory practices, as well as guidance for the dissertation for the Master's and Doctor's degrees, have been provided.

Undergraduate education

Lectures on biochemistry and molecular biology, with a focus on the diversity, structures and functions of lipids, for undergraduate medical students. Four undergraduate students (two M6 students and two M2 students) are now participating in the Murakami's team throughout the year. One MD/PhD course student has received the Dean's Award in 2024.

Publications

- Oishi Y, Koike H, Kumagami N, Nakagawa Y, Araki M, Taketomi Y, Miki Y, Matsuda S, Matsuzaka T, Ozawa H, Shimano H, Murakami M, Manabe I. Macrophage SREBP1 regulates skeletal muscle regeneration. *Front Immunol.* 14, 1251784, 2024.
- Hamu-Tanoue A, Takagi K, Taketomi Y, Miki Y, Nishito Y, Kano K, Aoki J, Matsuyama T, Kondo K, Dotake Y, Matsuyama H, Machida K, Murakami M, Inoue H. Group III secreted phospholipase A₂ -driven lysophospholipid pathway protects against allergic asthma. *FASEB J.* 38, e23428, 2024.
- Kudo K, Yanagiya R, Hasegawa M, Carreras J, Miki Y, Nakayama S, Nagashima E, Miyatake Y, Torii K, Ando K, Nakamura N, Miyajima A, Murakami M, Kotani A. Unique lipid composition maintained by extracellular blockade leads to prooncogenicity. *Cell Death Discov.* 10, 221, 2024.
- Horikiri K, Taketomi Y, Kondo K, Yamasoba T, Murakami M. Activation of the PGE₂-EP2 pathway as a potential drug target for treating eosinophilic sinusitis. *Front Immunol.* 15, 1409458, 2024.
- Taketomi Y, Higashi T, Kano K, Miki Y, Mochizuki C, Toyoshima S, Okayama Y, Nishito Y, Nakae S, Tanaka S, Tokuoka SM, Oda Y, Shichino S, Ueha S, Matsushima K, Akahoshi N, Ishii S, Chun J, Aoki J, Murakami M. Lipid-orchestrated paracrine circuit coordinates mast cell maturation and anaphylaxis through functional interaction with fibroblasts. *Immunity.* 57, 1828-1847.e11. 2024.
- Sato H, Taketomi Y, Murase R, Park J, Hosomi K, Sanada TJ, Mizuguchi K, Arita M, Kunisawa J, Murakami M. Group X phospholipase A₂ links colonic lipid homeostasis to systemic metabolism via host-microbiota interaction. *Cell Rep.* 243, 114752, 2024.
- Murakami M. Extracellular vesicles as a hydrolytic platform of secreted phospholipase A₂. *Biochim Biophys Acta Mol Cell Biol Lipids.* 1869, 159536, 2024. (Review)
- Suzuki T, Taketomi Y, Yanagida K, Yoshida-Hashidate T, Nagase T, Murakami M, Shimizu T, Shindou H. Re-evaluation of the canonical PAF pathway in cutaneous anaphylaxis. *Biochim Biophys Acta Mol Cell Biol Lipids.* 1870, 159563, 2024.
- Nakamura Y, Shimada IS, Maroofian R, Falabella M, Zaki MS, Fujimoto M, Sato E, Takase H, Aoki S, Miyauchi A, Koshimizu E, Miyatake S, Arioka Y, Honda M, Higashi T, Miya F, Okubo Y, Ogawa I, Scardamaglia A, Miryounesi M, Alijanpour S, Ahmadabadi F, Herkenrath P, Dafsari HS, Velmans C, Al Balwi M, Vitobello A, Denommé-Pichon AS, Jeanne M, Civit A, Abdel-Hamid MS, Naderi H, Darvish H, Bakhtiari S, Kruer MC, Carroll CJ, Ghayoor Karimiani E, Khailany RA, Abdulqadir TA, Ozaslan M, Bauer P, Zifarelli G,

- Seifi T, Zamani M, Al Alam C, Alvi JR, Sultan T, Efthymiou S, Pope SAS, Haginoya K, Matsunaga T, Osaka H, Matsumoto N, Ozaki N, Ohkawa Y, Oki S, Tsunoda T, Pitceathly RDS, Taketomi Y, Houlden H, Murakami M, Kato Y, Saitoh S. Biallelic null variants in PNPLA8 cause microcephaly by reducing the number of basal radial glia. *Brain*. 147, 3949-3967, 2024.
10. Sikder MM, Sasaki S, Miki Y, Nagasaki Y, Ohta KI, Hussain Z, Saiga H, Ohmura-Hoshino M, Hoshino K, Ueno M, Okada-Iwabu M, Murakami M, Ueda N, *Uyama T. PLAAT5 as an *N*-acyltransferase responsible for the generation of anti-inflammatory N-acylethanolamines in testis. *Biochim Biophys Acta Mol Cell Biol Lipids*. 1870, 159583, 2024.
11. Moutusy SI, Ohsako S. Gut Microbiome-Related Anti-Inflammatory Effects of Aryl Hydrocarbon Receptor Activation on Inflammatory Bowel Disease. *Int J Mol Sci*, 25, 3372, 2024.

Laboratory of Animal Resources

Professor

Atsu Aiba, Ph.D.

Lecturer

Yuichi Hiraoka, Ph.D.

Assistant Professor

Harumi Nakao, Ph.D., Ryo Saito, Ph.D., Shoko Noda-Narita M.D., Ph.D.

Homepage <http://lar.cdbim.m.u-tokyo.ac.jp/index.html>

Introduction and Organization

Our laboratory was established as the Division of Animal Research affiliated with the Faculty of Medicine in April 1971. The building for animal experimentation was completed and the accommodation and experimentation of laboratory animals started in 1973. In 2003, the laboratory was reorganized as the Section of Animal Research of the Center for Disease Biology and Integrative Medicine (CDBIM). In 2008, the Laboratory of Animal Resources was established to strengthen research activities in addition to the Section of Animal Resources. The members of our laboratory and section are 5 teaching staffs, 5 technical support staffs, a senior assistant manager, an administrative staff, an assistant laboratory animal technician, 3 assistant clerks and a temporary staff (veterinarian). In addition, about 10 contracted employees are involved in animal breeding and maintenance of the animal facility.

The laboratory animals in our facility include dogs, swine, rabbits, rats, mice, and marmosets. The number of registered users of our facility was 678 at the end of academic year 2023.

We provide quality care for all animals in our facility and assist animal experimentation carried out by the researchers. The office of our section is in charge of the secretariat of the Institutional Animal Care and the Use Committee (IACUC) of the Graduate School of Medicine, the University of Tokyo. The committee (Chair, Prof. Atsu Aiba) reviews the plans of animal

experimentation and helps researchers carry out animal experiments in accordance with law, regulations and University policies governing the use of animals.

Teaching activities

We are responsible for the education of laboratory animal science to the 2nd-year students (M0) of the Faculty of Medicine. The lecture includes animal welfare, refinement of animal experiments, animal breeding, infectious diseases of laboratory animals and zoonoses. We also give a lecture on mouse molecular genetics and molecular embryology.

We are also involved in lectures by IACUC for the researchers at the Graduate School of Medicine.

Research activities

Our laboratory focuses on understanding the molecular mechanisms which underlie brain function and brain metastasis. We also try to generate murine and marmoset models for human genetic diseases.

1. Generation and Analysis of Marmoset Models for Psychiatric Disorders

Common marmoset (*Callithrix jacchus*) is a non-human primate and recently used for human model, especially focusing on brain function. We have established a novel protocol in which embryos are collected from already mated females by oviduct

flushing and immediately transferred into the oviduct of the very same donors following injections with genome-editing components. Using this autologous transfer protocol, we aim to establish marmoset models for psychiatric disorders. We have successfully generated marmosets with mutations in four genes, including the FMR1 gene, which is responsible for fragile X syndrome that frequently causes autism, and the GRM5 gene, which encodes metabotropic glutamate receptor 5. These marmosets are currently under analysis.

Marmosets with FMR1 mutations, which lack expression of the FMRP protein encoded by FMR1, exhibit epilepsy-like seizures and die by day 11 after birth. However, introducing GRM5 mutations suppresses these phenotypes, providing evidence for the "mGluR hypothesis" of fragile X syndrome in non-human primates. Furthermore, by conducting EEG measurements on heterozygous FMR1 mutants, we have observed phenotypes that replicate abnormalities in auditory evoked potentials observed in fragile X syndrome and autism spectrum disorders.

2. Elucidating the neural basis of consolation behavior

Consolation behavior is affiliative social contact, for example, a hug to alleviate pain or stress experienced by another individual. In rodents, grooming behavior toward a distressed mate (allogrooming) is observed as a consolation-like behavior. The division also attempted to detect consolation-like behavior in inbred mice and constructed an experimental system to see comforting behavior prominently and efficiently. Currently, we are exploring which brain regions are involved in consolation-like behavior by whole-brain mapping of neural activity.

We are also focusing on the function of vasopressin which is known the posterior pituitary hormone, and have found that vasopressin 1a receptor (AVPR1a) knockout mice generated in our division display reduced allogrooming compared to wild-type mice. In the future, we plan to explore which brain regions express Avpr1a neurons that play an important role in consolation-like behavior.

3. Functional analysis of the blood-brain barrier in brain metastasis

The blood-brain barrier (BBB) plays an essential role in brain metastasis of cancer. Although the analysis of molecules required for brain metastasis on the cancer cell side has been well performed, the molecular mechanism of vascular endothelial cells, pericytes (mural cells) and astrocytes, which constitute the BBB, has not been elucidated. Therefore, we aim to reveal the molecular signaling involved in vascular permeability and cancer brain metastasis by reconstituting the BBB *in vitro* model using brain vascular endothelial cells, pericytes, and astrocytes and by genetically manipulating vascular endothelial cells in mice.

In vitro BBB model indicated the role of pericytes in both promoting and inhibiting the invasion of cancer cells. The mice with endothelial cell-specific knockout of focal adhesion kinase (FAK) also indicated the different metastatic mechanism between brain and trunk metastasis. The brain metastases in the endothelial cell-specific knockout mice of FAK were accelerated, although the metastases in the trunk have been reported to be suppressed.

Now we plan to elucidate the specific mechanism needed for brain metastasis by analyzing the interaction between cancer cells and BBB.

4. Understanding the contribution of glial cells in the brain function

Glial cells are non-neuronal cells in the central nervous system that perform various functions, ranging from supporting neurons to regulating activities. In recent years, the importance of this cell group has been rapidly recognized. Our department focuses on the diversity of glial cells, aiming to elucidate the mechanisms by which they contribute to higher brain functions. Currently, we are analyzing the functional diversity among different brain regions. Using genetically modified mice capable of specifically labeling glial cells in distinct brain regions, we conduct *in vivo* experiments to infer their physiological and pathological functions by observing the phenomena that occur when glial cells in various brain regions are modulated.

We have recently discovered that a rapid rise in body temperature is observed in mice where astrocytes, a

type of glial cell, are selectively activated in the hypothalamus. We are conducting further analyses using single-cell gene expression profiling to uncover the molecular mechanisms underlying this phenomenon.

References

- Nozawa O, Miyata M, Shiotani H, Kameyama T, Komaki R, Shimizu T, Kuriu T, Kashiwagi Y, Sato Y, Koebisu M, Aiba A, Okabe S, Mizutani K, and Takai Y.
Necl2/3-mediated mechanism for tripartite synapse formation.
Development, 150(4), dev200931, 2023.
- Toyoda Y, Miyata H, Uchida N, Morimoto K, Shigesawa R, Kassai H, Nakao K, Tomioka NH, Matsuo H, Ichida K, Hosoyamada M, Aiba A, Suzuki H, and Takada T.
Vitamin C transporter SVCT1 serves a physiological role as a urate importer: functional analyses and in vivo investigations.
Pflugers Arch, 475(4), 489-504, 2023.
- Hasegawa K, Takenaka N, Yamamoto M, Sakoda Y, Aiba A, and Satoh T.
Regulation of De Novo Lipid Synthesis by the Small GTPase Rac1 in the Adipogenic Differentiation of Progenitor Cells from Mouse White Adipose Tissue.
Int J Mol Sci, 24(5), 4608, 2023.
- Kodera T, Takeuchi RF, Takahashi S, Suzuki K, Kassai H, Aiba A, Shiozawa S, Okano H, and Osakada F.
Modeling the marmoset brain using embryonic stem cell-derived cerebral assembloids.
Biochem Biophys Res Commun, 657, 119-127, 2023.
- Kikuchi I, Iwashita Y, Takahashi-Kanemitsu A, Koebis M, Aiba A, and Hatakeyama M.
Coevolution of the ileum with Brk/Ptk6 family kinases confers robustness to ileal homeostasis.
Biochem Biophys Res Commun, 676, 190-197, 2023.
- Matsukawa T, Yagi T, Uchida T, Sakai M, Mitsushima M, Naganuma T, Yano H, Inaba Y, Inoue H, Yanagida K, Uematsu M, Nakao K, Nakao H, Aiba A, Nagashima Y, Kubota T, Kubota N, Izumida Y, Yahagi N, Unoki-Kubota H, Kaburagi Y, Asahara SI, Kido Y, Shindou H, Itoh M, Ogawa Y, Minami S, Terauchi Y, Tobe K, Ueki K, Kasuga M, and Matsumoto M.
Hepatic FASN deficiency differentially affects nonalcoholic fatty liver disease and diabetes in mouse obesity models.
JCI Insight, 8(17), e161282, 2023.
- Kanaya T, Ito R, Morizawa YM, Sasaki D, Yamao H, Ishikane H, Hiraoka Y, Tanaka K, and Matsui K.
Glial modulation of the parallel memory formation.
Glia, 71(10), 2401-2417, 2023.
- Onodera K, Tsuno Y, Hiraoka Y, Tanaka K, Maejima T, and Mieda M.
In vivo recording of the circadian calcium rhythm in Prokineticin 2 neurons of the suprachiasmatic nucleus.
Sci Rep, 13(1), 16974, 2023.
- Ishino F, Itoh J, Irie M, Matsuzawa A, Naruse M, Suzuki T, Hiraoka Y, and Kaneko-Ishino T.
Retrovirus-Derived *RTL9* Plays an Important Role in Innate Antifungal Immunity in the Eutherian Brain.
Int J Mol Sci, 24(19), 14884, 2023.

Laboratory of Molecular Radiology

Associate Professor

Noriko Hosoya, M.D., Ph.D.

Lecturer

Atsushi Enomoto, Ph.D.

Homepage <http://www.cdbim.m.u-tokyo.ac.jp/>

Introduction and Organization

When the Center for Disease Biology and Integrative Medicine was established in 2003, the Department of Radiation Oncology established in 1967 and the Radiation Research Institute established in 1992 were joined to form the Section of Radiation Biology as a part of Divisions of Research Resources and Support. In 2008, the Laboratory of Molecular Radiology was also established to strengthen research activities in this section. The scientists and staffs belong to both the section and the laboratory.

The aim of this laboratory is to facilitate translational research from frontier life science to applied radiology by introducing molecular biology into conventional radiology.

To maintain the facility of radiation research, responsible staffs at Graduate School of Medicine and the Tokyo University Hospital are elected from our section. Since the hospital radioisotope research facility has been continued to be closed since 2015, the facility in the Graduate School of Medicine widely accept the radioisotope users from the hospital as well as the other departments in the University of Tokyo.

Education

We are responsible for the education of basic radiation medicine for the 3rd year medical students. The students are expected to start with understanding of the physics and the chemistry for radiation and then understand the basic biology of radiation. Furthermore, they learn how to handle radioactive materials by the 2-day practical course.

In addition to these courses, the 4th year medical students are expected to learn how to use clinical radiation technology safely in hospitals. The background for this addition is that clinical problems arising from the lack of knowledge of radiation effects have been increasing. Furthermore, the education of radiation emergency medicine is included in this course. Even though radiation casualty is rare, all clinicians should know how to treat patients exposed to radiation. The importance of this education has been widely recognized since the accident at the Fukushima nuclear power plant.

We also take part in the education of radiation health science for the 3rd year students specialized in integrated health sciences. Radiation protection is emphasized in this course.

For graduate students, the education of molecular biology of the DNA damage response to radiation and DNA repair is more intensively integrated.

In addition, education courses for users of radioactive materials frequently take place.

Research

We focus on the mechanism underlying the cellular response to DNA double-strand breaks (DSBs). Among various types of DNA damage, DSBs are the most deleterious if not repaired properly. To protect the genome, at least four signaling cascades are known to function as the repair machineries against DSBs. While nonhomologous end joining, microhomology-mediated end joining, and single-strand annealing are error-prone repair pathways, homologous recombination (HR) is an error-free

pathway in principle using newly replicated DNA as a template for the repair. There is accumulating evidence that defective HR plays a role in tumor development. For example, BRCA1 and BRCA2, tumor suppressors in hereditary breast and ovarian cancers, are known to mediate the damage response to DSBs and promote HR.

RAD51, a key player at early stages of HR, catalyzes the invasion of a single-strand DNA end into an intact homologous duplex. BRCA2 plays a mediator role at this stage by directly binding to Rad51 and promoting the formation of the filament consisting of the single-strand DNA and RAD51.

SYCP3 is a component in the synaptonemal complex which is formed between homologous chromosomes to ensure their connection in meiosis. Expression of SYCP3 was observed in adrenal, liver, stomach, and kidney tumors, confirming that SYCP3 is a cancer testis antigen. Treatment of SYCP3-nonexpressing cells with a methylation inhibitor induced its expression, indicating that methylation alteration in cancer is responsible for its ectopic expression.

Since biological significance of cancer testis antigens in somatic cells is largely unknown, we investigated the effects of SYCP3 expression on cellular functions in somatic cells. This study revealed that SYCP3-expressing cells are hypersensitive to radiation and cisplatin and are characterized by increased aneuploidy. As these phenotypes are consistent with those of defective HR, we screened the molecule that co-localizes with SYCP3 by immunofluorescence. Consequently, we identified that the tumor suppressor BRCA2 co-localizes with SYCP3. We also confirmed that these proteins form a complex. Furthermore, we found that binding of SYCP3 to BRCA2 inhibits the HR repair activity mediated by binding of BRCA2 to RAD51.

Since cells with BRCA1 or BRCA2 mutations are hypersensitive to PARP inhibitors, their clinical trials are internationally ongoing. However, the problem is that the application of the trial is limited due to low incidence of their mutations. Our findings implicate that SYCP3-expressing cancers, even if they do not harbour BRCA mutations, are sensitive to PARP inhibitors, providing novel insight into cancer therapy based on the synthetic lethal approach in which both

two pathways essential for cell viability are disrupted by an intrinsic genetic alteration and a specific pathway inhibitor.

SYCE2, a component constituting the synaptonemal complex, is also expressed at varying levels in somatic cells. SYCE2 insulates heterochromatin protein 1 α from trimethylated histone H3 lysine 9 to promote ATM-dependent DNA double-strand break repair. This finding suggests that SYCE2 plays a role in the link between the nuclear microenvironment and the DNA damage response in somatic cells.

Radiation therapy and many DNA-damaging chemotherapeutic agents induce DNA DSBs, which can be normally repaired by the intrinsic repair pathways. The induced breaks therefore do not always lead to apoptosis. The studies on the mechanisms underlying the regulation of DNA damage response and repair in cancer will contribute to the establishment of novel therapeutic strategies against cancer. In order to develop therapeutic strategies for broader incurable diseases in an integrated manner, we are now extending our research on the mechanisms for the maintenance of genome stability in the cytoplasm.

Publications

1. Morgan C, Nayak A, Hosoya N, Smith GR, Lambing C. Structural chromosome organisation and its role in DNA repair, meiosis and diseases. *Curr Top Dev Biol*, 151:91-126, 2023.
2. Fukasawa T, Yamashita T, Enomoto A, Norimatsu Y, Toyama S, Yoshizaki-Ogawa A, Tateishi S, Kanda H, Miyagawa K, Sato S, Yoshizaki A. *Front Immunol*, 14:1286251, 2023.
3. Fukasawa T, Yamashita T, Enomoto A, Toyama S, Yoshizaki-Ogawa A, Tateishi S, Kanda H, Miyagawa K, Sato S, Yoshizaki A. Utility of nailfold capillary assessment for predicting pustulotic arthro-osteitis in palmoplantar pustulosis based on a prospective cohort study. *J Am Acad Dermatol*, 89:984-991, 2023.

Laboratory of Biomedical Informatics

Associate Professor

Takeshi Imai, Ph.D.

※The following information is the same as that of the previous year for certain reasons.

Homepage <http://www.cdbim.m.u-tokyo.ac.jp/>

Introduction and Organization

When the Center for Disease Biology and Integrative Medicine was established in 2003, Section of Biomedical Informatics was launched as one of the departments in Division of Research Resources & Support. In 2017, Laboratory of Biomedical Informatics was established as a part of Division of Research in the Center. Because of the parallel establishments, the both of organizations are made up of the same faculties.

The objective of Laboratory of Biomedical Informatics which is placed in the interdisciplinary field between medicine, engineering and informatics is to offer feedback to clinical medicine and contributions toward the healthcare and our society through studies such as analyses of medical information, gaining medical findings in secondary use of medical information, and developing and applying diagnosis support systems. Besides the studies, our laboratory takes a roll of graduate education for the doctor's program in the Department of Biomedical Informatics at the Division of Social Medicine, the master's program in the Medical Science Graduate Program, and the School of Public Health, the Graduate School of Medicine.

Section of Biomedical Informatics, Division of Research Resources & Support has an operation of the Office for Information Services, Graduate School of Medicine to maintain MERCS (Medical Research infrastructure with Computer System). The operations include: (1) handling the incidents of CERT and

maintaining network infrastructure, (2) offering software service of medical research supports, (3) operating mailing service for Faculty of Medicine, (4) operating DNS service and allocating global IP addresses for UT-Net connections, (5) operating web sites and servers of Faculty of Medicine and the Graduate School of Medicine, (6) offering learning devices at the medical library, and so on.

Teaching activities

In 2020, we took charge of lectures: "Description and Processing of Medical Knowledge" in the 2-year master course in the Medical Science Graduate Program, "Natural Language Processing and Computer Processing of Medical knowledge" in School of Public Health course, and "ICT and AI applications in Medicine" in the Lecture of Overview of Biomedical Engineering.

We accept students in the 2-year master course in the Medical Science Graduate Program, and 4-year Medical Sciences doctoral course, cooperating with teaching staffs in other laboratories in the field of medical informatics. Three students in the doctor's program, one student in the master's program, and two visiting researchers are enrolled in our laboratory in FY2020. Additionally, six undergraduate students took practice education in our laboratory through M3 Elective Clerkship program. We also accepted five graduate students from Toyama University as short-term intern.

Research activities

Our primary research domains are: (1) methods to knowledge representation and processing knowledge in healthcare, (2) analysis of electronic medical records and gaining medical knowledge with natural language processing and machine learning, (3) developing diagnosis support system, (4) standardization in the field of healthcare informatics, and so on.

In these domains, major research topics are listed below:

(1) Development of Medical Knowledge Infrastructure.

A large amount of medical information has been accumulated with the prevalence of computerization in medicine. Correspondingly, the needs of secondary use of the accumulated information for diagnosis support system and gaining medical knowledge have been increasing. Ontology, knowledge database, which is assembled mass of information describing the relationship of terms and concepts marshaled in a structured manner, is required for the study besides the techniques of machine learning and knowledge deduction. We have developed the clinical ontologies in particular fields such as anatomy, diseases, and abnormal status, as a funded research by the Ministry of Health, Labor and Welfare, Japan. For example, the ontology for diseases has been developed with approximately 6,000 diseases, that they are described as causal chains of abnormal states. We have also participated in “Research and development of intellectual information system infrastructure in medicine” project, sponsored by AMED since 2015. As further developing the ontology, we have worked on the study that clinical information of a targeted patient is automatically mapped on chronic disease ontology in order to perceive changes of disease states.

(2) Development of Diagnosis Support System for General Physicians.

It is difficult in community medicine to promote cooperation between medical experts and the core medical institutions. The experts of regional communities are required to have

comprehensive diagnosis skills and technical knowledge in the domain they specialize in. However, given the difficulty of such a situation that physicians take all the responsibilities, depending on only their knowledge and experiences, the need of diagnosis support system is pointed out. In this study, we have developed support system, that gives physicians in outlying regions access to refer to information matching experiences and knowledge matured general physicians have, to solve the issues. This project has been launched sponsored by AMED since January 2017. The current developed system is made up of approximately 20,000 case reports in internal medicine. The reports are transformed into knowledge database, described as chains of clinical states, so that the system can suggest a list of candidate diseases corresponding to a query, with certainty scores and reasons. The system (“J-Casemap”) was released and socially implemented as a service for members of the Japanese Society of Internal Medicine in August 2020. We also have worked on a study to automatically extract knowledge from raw texts in case reports using natural language processing for the continuous updating of the system.

(3) Analysis of Electrocardiogram (ECG) by Deep Learning.

Automatic analyzers of ECG data used in most hospitals are rule-based models that outputs ECG data in waveforms with clinical annotations. However, it still has difficulties on classification on abnormal findings. In fact, it is pointed out that it has a low sensitivity or potential for a false-positive diagnosis. Therefore, it needs an enhancement in its classification performance. We have developed another classification model using deep learning, intended for standard 12-leads ECG data. The current clinical annotations used for training our model is the ones given by the automatic analyzers; however we plan to apply diagnosis confirmed by echocardiogram as annotation data in future, so that our proposed model can be specialized in more specific abnormal findings

and achieve comparable performance to diagnosis by experts.

In addition to the researches, we have worked on other studies such as automatic selection of the underlying cause of death from death certificates using machine learning, and developing prescription support system in medical care for hypertension patients based on the clinical guidelines. Furthermore, we also have promoted a project aimed at the application of ICD-11 released in June 2018 for domestic use in Japan.

References

1. Iwai S, Mitani T, Hayakawa J, Shinohara E, Imai T, Kawazoe Y, Ohe K. Development of Graph-Based Algorithm for Differentiating Pathophysiological Conditions. *Applied Medical Informatics*. 2020;42(2):107-117.
2. Mitani T, Doi S, Yokota S, Imai T, Ohe K. Highly accurate and explainable detection of specimen mix-up using a machine learning model. *Clin Chem Lab Med*. 2020 Feb 25;58(3):375-383.
3. Imai T, Myojin T, Oigawa H, Kagawa R, Imamura T. Research on the actual situation and problems of determining the primary cause of death, and the applicability and challenges of machine learning for improving accuracy and efficiency. *Journal of Health and Welfare Statistics*. 2020;67(3):17-24. (In Japanese).
4. Imai T. Application of Artificial Intelligence Technology in the Field of Medical Natural Language Processing. *Journal of the Japanese Society for Artificial Intelligence*. 2020;35(4): 474-479. (In Japanese).
5. Imai T. ICD-11 as a clinical terminology and issues for the application in Japan. *Japan Journal of Medical Informatics*. 2020; 40(suppl.): 324-327. (In Japanese).
6. Ogawa T, Imai T, Takizawa M, Komatsu M, Imamura T. Consideration of Japanese translations for the domestic application of ICD-11 in Japan. *Japan Journal of Medical Informatics*. 2020; 40(suppl.): 328-331. (In Japanese).
7. Ogishima S, Imai T, Yoshida T, Ohara O, Tsutsumi M, Furuta K, Nakagome H, Nishimura K. Standardization of clinical sequence data. *Japan Journal of Medical Informatics*. 2020; 40(suppl.): 371-373. (In Japanese).
8. Myojin T, Oigawa H, Kagawa R, Imamura T, Imai T. Extraction of issues in determining the underlying cause of death in Japan to improve the accuracy and efficiency of cause-of-death statistics. *Japan Journal of Medical Informatics*. 2020; 40(suppl.): 674-676. (In Japanese).
9. Oigawa H, Myojin T, Kagawa R, Imamura T, Imai T. Feasibility of Domestic Use of Iris in the Determination Process of the Underlying Cause of Death. *Japan Journal of Medical Informatics*. 2020; 40(suppl.): 677-682. (In Japanese).

The International Research Center for Medical Education (IRCME)

Department of Medical Education Studies

Professor

Masato Eto, M.D., Ph.D.

Lecturer

Masashi Izumiya, M.D., Ph.D.

History and organization

International Research Center for Medical Education, established in 2000, had functioned as a center for the whole university and kept relations with Graduate School of Medicine in various ways. IRCME became an affiliated center for education and research under the control of Graduate School of Medicine since April 2013. IRCME previously consisted of two departments of International Cooperative Study in Medical Education, and Planning & Cooperation for International Cooperative Projects and Information on Medical Education. Names of two new departments are Department of Medical Education Studies and Department of International Cooperation for Medical Education.

The mission of Department of Medical Education Studies includes promotion of medical education not only in Faculty of Medicine of the University of Tokyo but also of the whole country. Specific contents are as follows:

- (1) Research in medical education and dissemination within and outside of the University

Medical and health professions education needs to continue revisions to meet health care needs of the country or the region. However, since every country or region has different culture or social system, experiences to apply updated evidence to the real settings to revise the system.

- (2) Support to undergraduate and postgraduate education in the University

Through the support to education in Faculty of

Medicine and the University Hospital, we show the effectiveness of such teaching practice and apply it to other medical schools in Japan for future reform.

Activities

This department promotes research related to medical education field. As the studies of medical education develop very rapidly all over the world, the department expands research to construct theories and emphasizes activities of educational practice or improvement.

In the University, this department provides information and members as to the education of Faculty of Medicine in such as academic affair committee, medical education reform working group, and clinical clerkship. Moreover, the department offers educational activities such as PBL (problem-based learning) and clinical skill practical training. The department operates OSCE (objective structured clinical examination). The department also runs and manages “Tsutsuji no kai” under the consortium with Institute of Science Tokyo to develop simulated patients indispensable for education of medical interview.

This department promotes practical activities for the pre-graduate education of medical students and research in fields related to medical education. In the field of pre-graduate education, the department aims to nurture and produce human resources who can lead medicine and medical care in Japan, as well as to provide educational content of international standard. In addition, against the backdrop of the rapid

development of digital technology in recent years, the department will conduct research to provide effective and efficient medical education utilizing these new technologies.

The faculty members of this division are active members of the Academic Affairs Committee, working groups on educational reform, clinical clerkships, and other committees related to education at the Faculty of Medicine. The department also conducts PBL tutorials, clinical introductory training, and interprofessional education (IPE) in collaboration with other departments and universities. Furthermore, the department is focusing on simulation education for medical students using the clinical simulation center organized in the University of Tokyo Hospital. The department is also in charge of the administration of the OSCE (objective structured clinical examination) and post-clinical clerkship examination with the Educational Affairs of Administrative Division. In addition, the department operates and manages the *Tsutsuji no kai*, a consortium with Tokyo Medical and Dental University, to train simulated patients, which is essential for medical interviewing education.

The department is also in charge of conducting institutional research (IR), class/curriculum surveys and peer observation of classroom for continuous evaluation and improvement of medical education, as well as the administrative office of the Medical Education Improvement Committee.

Department of International Cooperation for Medical Education

Assistant Professor

Hiroataka Onishi, M.D., M.H.P.E., Ph.D.

※The following information is the same as that of the previous year for certain reasons.

Homepage <https://www.icme.m.u-tokyo.ac.jp/home>

Introduction and Organization

International Research Center for Medical Education (IRCME), established in 2000, had functioned as a center for the whole university and kept relations with Graduate School of Medicine in various ways. IRCME became an affiliated center for education and research under the Graduate School of Medicine umbrella since April 2013. IRCME currently consists of the Department of Medical Education and the Department of International Cooperation for Medical Education (ICME). Since April 2018, the Department of International Cooperation in Medical Education, which had been operated in an integrated manner with the Department of Medical Education, has been operated independently. It is one of the departments of the IRCME, and encompasses international cooperation in areas related to medical education, as well as practice and research in areas that connect policies and actual clinical practice, such as global health, community medicine, and general practice.

Education

The Department of ICME offers classes as cooperative department for School of International Health (SIH) and School of Public Health (SPH). In SIH special lectures of international cooperation for medical education are offered twice a year (spring and autumn). In SPH the class in spring is human resource

development in health and medical practice and the class in autumn is learner assessment.

Since 2019, several graduate students are studying in ICME, and weekly seminars are provided every Wednesday.

Research

(1) International Cooperation in the Field of Health Professions Education: Through participation in international cooperation projects in Asia and other countries, we explore what education and policies in the health and medical fields should be like. He is also involved in surveys and research on the accepting medical and nursing professionals from overseas and on cultural and language frictions. Through joint research with related institutions in Taiwan and Indonesia, we aim to gain experience in evaluation methods, policy recommendations, and coordination among related parties, as well as to disseminate the research results and become a core research center in this field.

(2) Study on Learner Assessment: When certifying the completion of the program, it is very important to investigate how the learner's assessment is conducted and how the pass/fail decision is made. Various changes are seen in the concept of assessment itself. Current studies include the development of work-based assessment methods, verification of reliability

and validity of assessment tools, and the improvement of methods for standard setting of pass/fail judgment criteria.

(3) Research related to ACP (advance care planning): We continue researching how and where the elderly want to end their own life and the relationship between their family's thoughts.

(4) Practice and research in the field linking health policy and clinical practice: Studies are done for how to train the professionals contributing to community-based integrated care system.

References

1. Schuwirth L, Colliver J, Gruppen L, Kreiter C, Mennin S, Onishi H, ... & Wagner M. Research on Assessment Practices. In International Best Practices for Evaluation in the Health Professions (pp. 59-75). CRC Press; 2022
2. Tsuchida T, Onishi H, Ono Y, Machino A, Inoue F, & Kamegai M. Factors associated with preferred place of death among older adults: a qualitative interview study in Tama City, Tokyo, Japan. *BMJ open*. 2022; 12(5): e059421.
3. Ernawati DK, Sutiari NK, Astuti IW, Onishi H, & Sunderland B. Correlation between intercultural sensitivity and collaborative competencies amongst Indonesian healthcare professionals. *Journal of Interprofessional Education & Practice*. 2022; 29: 100538.

Global Nursing Research Center

Director, Professor

Noriko Yamamoto-Mitani, Ph.D., R.N., FAAN

Vice Director, Professor

Megumi Haruna, Ph.D., R.N.M., R.N.

Mari Ikeda, Ph.D., R.N., C.C.P.

Project Senior Lecturer

Sameh Eltaybani, Ph.D.

Kojiro Morita, Ph.D., M.P.H., R.N., P.H.N.

Project Assistant Professor

Noyuri Yamaji, Ph.D., R.N., P.H.N.

Project Researcher

Asa Inagaki-Asano, Ph.D., R.N., P.H.N.

Daijiro Haba, Ph.D., R.N., P.H.N.

Riko Otori, Ph.D., R.N., P.H.N.

Taisuke Yasaka, Ph.D., R.N., P.H.N.

Homepage <https://gnrc.m.u-tokyo.ac.jp/en/>

Introduction and Organization

With a falling birthrate and a super-aging society, Japan is in need of a paradigm shift toward medical and nursing care that supports aging, as well as those dealing with chronic health conditions, to lead lives with maximum independence and well-being. In order to provide a healthy life expectancy for its people, it will be necessary for Japan to face its forthcoming challenges and bring about the realization of a 'care' society that lightens the difficulties of daily living and brings a self-reliant way of life to the Japanese nation. Nursing, which plays a central role in providing care, must evolve into a science for the realization of this 'care' society. Currently, however, the dominant paradigm employed in various nursing fields embraces a structure that supports the training of clinical nurses, not the development of a science aimed at producing medical and nursing care that supports individuals and

communities. Thus, GNRC seeks to promote research into an innovative, transdisciplinary nursing science that systematizes this type of care. In particular, our focus is to create transdisciplinary research and educational environment that fosters young leaders in nursing research who will promote care innovation and develop nursing systems for implementation.

In order to achieve this, we must work toward integrating nursing with fields it has yet to fully collaborate with, such as bio-engineering, molecular biology, human engineering, philosophy, educational psychology, information science, and policy science. Moreover, as the field of nursing science continues to develop, further attention must be paid to the development of human resources necessary to promote this transdisciplinary research and the networks necessary to create collaborative relationships among industry, government, and academia. In short, our aim

is to create a long-term research system that allows young researchers to conduct transdisciplinary work ranging from fundamental research to studies with commercial applications.

Thus, the Global Nursing Research Center has been established as an affiliated research center, which is the first of its kind in nursing science in Japan. The GNRC will continue to execute the following three goals:

- 1) Establishing an innovative nursing research field through transdisciplinary integration,
- 2) Conducting cutting-edge research alongside aspiring young researchers and disseminating findings globally, and
- 3) Developing academic and educational frameworks to establish foundations for these new fields.

Establishing an Innovative Nursing Research Field

1. Division of Care Innovation

The Division of Care Innovation promotes various research activities, such as robotics nursing, biological nursing, visualized nursing, clinical nursing technology and reverse translational research, with the aim of developing and producing patient care products that lighten unfavorable conditions of daily life due to the health impairment of each person.

2. Division of Nursing Systems

The Division of Nursing Systems promotes such research activities as health-quality outcome research and care quality management, in order to provide nursing practice solutions that reflect important cultural and social concerns, construct Japan-origin nursing theories that support high-quality practices, and make policy proposals.

3. Division of Global Collaborative Research

The Division of Global Collaborative Research promotes collaborative research and creates a network of research groups among global partners to resolve global health issues and create a platform to share and increase the visibility of our outcomes locally and internationally.

4. Achievements

In 2023, our achievements included the initiation of three international collaborative research projects, one

patent application, and one collaborative research project with industry, as well as 60 English publications.

Conducting Innovative Nursing Research

1. International Invited Faculty

In 2023, we invited four international researchers who provided consultations to our graduate students and post-doctoral researchers on their research projects.

2. Post-doctoral Program

Post-doctoral (PD) researchers engage in focused research projects, the findings of which will be made known to the public. PD researchers take seven essential seminars covering comprehensive research knowledge, skills, and global awareness: (1) Leadership in Nursing and Healthcare, (2) English Writing and Presentation, (3) Bioengineering Nursing, (4) Analysis of Real World Data, (5) Qualitative Research, (6) Community-Based Participatory Research, and (7) Developing Multicenter Cohort and International Collaborative Research.

In 2023, four PD researchers participated in this program.

3. GNRC Seminars and Special Lectures

In 2023, we organized 15 seminars and special lectures featuring professors from Japan and abroad, with a total of 509 participants, including students and faculty members from the University of Tokyo and other institutions.

4. Other activities

In 2023, we organized the “Hongo Summer Dojo at UTokyo,” as a hybrid event, inviting nursing researchers from Japan and abroad. The program aimed to enhance inter-university collaboration and foster international collaborative research by providing a platform for presenting and exchanging nursing research. A total of 77 faculty members and graduate students from 11 universities participated. As part of our broader efforts toward international collaborative research, eight faculty members visited the University of Tokyo New York Office, Columbia University, Yale University, and Children's National Hospital in the United States. In October, our Director, Professor Noriko Yamamoto-Mitani, was inducted as the eighth Japanese Fellow of the American Academy of Nursing

(FAAN), a prestigious recognition for leaders in nursing education, practice, and research. The annual Spring International Program was also held to provide an opportunity for graduate students from Japan and abroad to learn and share innovative approaches and methodologies in nursing science. Participants included 38 graduate students and nursing faculty from our university, as well as 28 graduate students and faculty from 14 universities abroad.

Establishing Foundations for Future Nursing Research

1. Global Nursing Research Center Fund

The Global Nursing Research Center Fund continued to support the employment and development of postdoctoral fellows and other emerging researchers.

Selected Publications

1. Eltaybani, S. (2023). Capabilities and limitations of large language models in critical care nursing research: Examples from the big three. *Nursing in Critical Care*, 28(6), 838–853. <https://doi.org/10.1111/nicc.12974>
2. Eltaybani, S., Igarashi, A., Cal, A., Lai, C. K. Y., Carrasco, C., Sari, D. W., ..., Yamamoto-Mitani, N. (2023). Long-term care facilities' response to the COVID-19 pandemic: An international, cross-sectional survey. *Journal of Advanced Nursing*. <https://doi.org/10.1111/jan.15785>
3. Eltaybani, S., Kawase, K., Kato, R., Inagaki, A., Li, C. C., Shinohara, M., Igarashi, A., Sakka, M., Sumikawa, Y., Fukui, C., & Yamamoto-Mitani, N. (2023). Effectiveness of home visit nursing on improving mortality, hospitalization, institutionalization, satisfaction, and quality of life among older people: Umbrella review. *Geriatric Nursing*, 51(1), 330–345. <https://doi.org/10.1016/j.gerinurse.2023.03.018>
4. Eltaybani, S., Kitamura, S., Fukui, C., Igarashi, A., Sakka, M., Noguchi-Watanabe, M., Takaoka, M., Inagaki, A., Yasaka, T., Kobayashi, H., & Yamamoto-Mitani, N. (2023). Toward developing care outcome quality indicators for home care for older people: A prospective cohort study in Japan. *Geriatrics & Gerontology International*, 23(5), 383–394. <https://doi.org/10.1111/ggi.14578>
5. Morita, K., Matsui, H., Ono, S., Fushimi, K., & Yasunaga, H. (2023). Association between better night-shift nurse staffing and surgical outcomes: A retrospective cohort study using a nationwide inpatient database in Japan. *Journal of Nursing Scholarship*, 55(2), 494–505. <https://doi.org/10.1111/jnu.12845>
6. Morita, K., Miyamoto, Y., Mizuno, A., Shirane, S., Ohbe, H., Hashimoto, Y., Kaneko, H., Matsui, H., Fushimi, K., & Yasunaga, H. (2023). Impact of a financial incentive scheme for team-based palliative care in patients with heart failure in Japan: A nationwide database study. *International Journal of Cardiology*. <https://doi.org/10.1016/j.ijcard.2023.131145>
7. Hamasaki, Y., Sakata, N., Jin, X., Sugiyama, T., Morita, K., Uda, K., Matsuda, S., & Tamiya, N. (2023). Facility staffing associated with potentially avoidable hospitalizations in nursing home residents in Japan: A retrospective cohort study. *BMC Geriatrics*, 23(1), 566. <https://doi.org/10.1186/s12877-023-04066-3>
8. Ishibashi, T., Kaneko, H., Ueno, K., Morita, K., Itoh, H., Okada, A., Kamiya, K., Suzuki, Y., Matsuoka, S., & Fujiu, K. (2023). Association between early initiation of cardiac rehabilitation and short-term outcomes of patients with acute heart failure admitted to the intensive care unit. *The American Journal of Cardiology*, 206, 285–291. <https://doi.org/10.1016/j.amjcard.2023.06.012>
9. Yamaji, N., Kobayashi, K., Hasegawa, D., & Ota, E. (2023). Developing and evaluating a cancer communication picture book for children, families, and healthcare professionals: A mixed methods feasibility study. *Asia-Pacific Journal of Oncology Nursing*. <https://doi.org/10.1016/j.apjon.2023.100345>
10. Nishio, H., Ohde, S., Yamaji, N., & Takahashi, O. (2023). Factors associated with patients' ratings of hospitals among Japanese inpatients: A cross-sectional study. *JMA Journal*, 6(2), 148–155. <https://doi.org/10.31662/jmaj.2022-0176>
11. Yoshioka-Maeda, K., Matsumoto, H., Inagaki-Asano, A., & Honda, C. (2023). Community-based hip screening for up to four-month-old infants and health guidance for their caregivers in Japan: A nationwide survey. *Nursing Reports*,

- 13(4), 1442–1451. <https://doi.org/10.3390/nursrep13040121>
12. Haba, D., Qin, Q., Takizawa, C., Tomida, S., Minematsu, T., Sanada, H., & Nakagami, G. (2023). Local low-frequency vibration accelerates healing of full-thickness wounds in a hyperglycemic rat model. *Journal of Diabetes Investigation*. <https://doi.org/10.1111/jdi.13567>
13. Haba, D., Ohmiya, T., Sekino, M., Takizawa, C., Qin, Q., Tomida, S., Minematsu, T., Sanada, H., & Nakagami, G. (2023). Efficacy of wearable vibration dressings on full-thickness wound healing in a hyperglycemic rat model. *Wound Repair and Regeneration*. <https://doi.org/10.1111/wrr.13000>
14. Nishihara, N., Haruna, M., Usui, Y., Yonezawa, K., Hikita, N., Sasagawa, E., Nakano, K., Tanaka, M., Ohori, R., Aoyama, S., Sasaki, S., Fujita, M., Matsuzaki, M., Suetsugu, Y., & Sato, Y. (2023). Dietary intake and its association with birth outcomes in women with nausea and vomiting during the second trimester of pregnancy: A prospective cohort study in Japan. *Nutrients*, 15(15), 3383. <https://doi.org/10.3390/nu15153383>
15. Yoshimura, M., Fujita, M., Shibata, A., Ohori, R., Aoyama, S., Yonezawa, K., Sato, Y., Sasaki, S., Matsuzaki, M., Suetsugu, Y., & Haruna, M. (2023). Association of eicosapentaenoic and docosahexaenoic acid intake with low birth weight in the second trimester: The Japan Pregnancy Eating and Activity Cohort Study. *Nutrients*, 15(22), 4831. <https://doi.org/10.3390/nu15224831>

Center for Diversity in Medical Education and Research

Director/Professor

Kiyoto Kasai, M.D., Ph.D.

Vice Director/Associate Professor

Yoshihiro Satomura, M.D., Ph.D.

※The following information is the same as that of the previous year for certain reasons.

Homepage <https://cdmer.jp>

Introduction and Organization

The University of Tokyo Center for Diversity in Medical Education and Research was established in April 2021. The main purpose of the center is to promote education and research on diversity and inclusion in medicine. As part of this, the center aims to provide training programs for medical students with disabilities.

The center is working on the education, support, research and organizational change/ co-production divisions in close collaboration with the Graduate School of Medicine and Faculty of Medicine and Disability Services Office in the University of Tokyo. The center aims to improve the quality of patient-centered medical services by the inclusion of medical professionals with disabilities in the team medical care.

Education

Through education on diversity and inclusion in medicine, we will develop medical personnel including physicians and medical researchers who understand the significance of patient-public involvement (PPI) in medical research and development, and who have a co-production mindset in medical research and practice. For this purpose, we will be giving lecture to medical students in some of the existing educational programs.

For a more integrated and systematic education on diversity and inclusion in medicine, we are preparing

to establish the “Human Resource Development Program for Diversity and Inclusion in Medicine”. In this program, participating students will take the initiative in deepening their learning based on the philosophy of co-production and will not only be exposed to academic theory, but also participate in the practical field.

Research

There are many research issues that need to be clarified in order to promote diversity and inclusion in medicine. The actual situation regarding the presence rate of personnel with disabilities, and reasonable accommodation in medical education and practice settings needs to be clarified. Research on stigma held by health care providers, considered one of the most significant barriers to participation of medical personnel with disabilities, and the development of anti-stigma educational intervention methods are also needed. We will also need to explore the conditions for organizations in which personnel with disabilities can play an active role safely.

Publications

1. Yamagishi M, Satomura Y, Sakurada H, Kanehara A, Sakakibara E, Okada N, Koike S, Yagishita S, Ichihashi K, Kondo S, Jinde S, Fukuda M, Kasai K: Retrospective Chart Review-based Assessment

- Scale for Adverse Childhood Events and Experiences. *Psychiatry and Clinical Neurosciences Reports* 1: e58, 2022. 17 November 2022. <http://dx.doi.org/10.1002/pcn5.58>
2. Kanehara A, Morishima R, Takahashi Y, Koike H, Usui K, Sato S, Uno A, Sawai Y, Kumakura Y, Yagishita S, Usami S, Morita M, Morita K, Kanata S, Okada N, Yamasaki S, Nishida A, Ando S, Koike S, Shibuya T, Joseph S, Kasai K: Young carers in Japan: Reliability and validity testing of the BBC/University of Nottingham young carers survey questionnaire and prevalence estimation in 5,000 adolescents. *Psychiatry and Clinical Neurosciences Reports*. 1: e46, 2022. Sep 2022. DOI: 10.1002/PCN5.46
 3. Kiyono T, Ando S, Morishima R, Fujikawa S, Kanata S, Morimoto Y, Endo K, Yamasaki S, Usami S, Hiraiwa-Hasegawa M, Nishida A, Kasai K: Sex-based differences in the longitudinal association between autistic traits and positive psychotic experiences in adolescents: A population-based cohort study. *Schizophrenia Research*. 2022 Aug;246:1-6. doi: 10.1016/j.schres.2022.05.027.PMID: 35696856
 4. Morishima R, Koike H, Kanehara A, Usui K, Okada N, Ando S, Kasai K: Implementation of online classes during national school closure due to COVID-19 and mental health symptoms of adolescents: A cross-sectional survey of 5000 students. *Psychiatry and Clinical Neurosciences Reports*. June 2022. <https://doi.org/10.1002/pcn5.17>
 5. Kanehara A, Koike H, Fujieda Y, Yajima S, Kabumoto A, Kumakura Y, Morita K, Miyamoto Y, Nochi M, Kasai K: Culture-dependent and universal constructs and promoting factors for the process of personal recovery in users of mental health services: Qualitative findings from Japan. *BMC Psychiatry*. 2022 Feb 10;22(1):105. doi: 10.1186/s12888-022-03750-4.
 6. Kasai K, Kumagaya S, Takahashi Y, Sawai Y, Uno A, Kumakura Y, Yamagishi M, Kanehara A, Morita K, Tada M, Satomura Y, Okada N, Koike S, Yagishita S: "World-Informed" neuroscience for diversity and inclusion: An organizational change in cognitive sciences. *Clin EEG Neurosci*. 2022 Jun 12. PMID: 35695218 DOI: 10.1177/15500594221105755.
 7. Kasai K, Yagishita S, Tanaka SC, Koike S, Murai T, Nishida A, Yamasaki S, Ando S, Kawakami N, Kanehara A, Morita K, Kumakura Y, Takahashi Y, Sawai Y, Uno A, Sakakibara E, Okada N, Okamoto Y, Nochi M, Kumagaya SI, Fukuda M: Personalized values in life as point of interaction with the world: Developmental/neurobehavioral basis and implications for psychiatry. *Psychiatry Clin Neurosci Rep* 1: e12, June 2022. DOI:10.1002/pcn5.12.

Office of International Academic Affairs

Head

Shinichi Sato

Assistant Professors

Keiko Nanishi

David Kipler

Florence Ene

Homepage: <http://koryu.m.u-tokyo.ac.jp>

Status and functions

The Office of International Academic Affairs (OIAA) is under the direct supervision of the Dean of the Faculty of Medicine. Its three principal roles, as defined by the Committee on International Academic Affairs, are 1) facilitating international academic exchange, 2) overseeing international academic and research agreements, and 3) supporting education and research activities.

Activities

This report details the activities of the OIAA during the 2023-24 academic year (1 April 2023 through 31 March 2024).

1. International Academic Exchange

1.1 Support for International Students

The OIAA assists international students in applying for various scholarships, and the OIAA on-campus screening committee evaluates applicants for scholarships that require a university recommendation. To promote friendship among international students, the OIAA hosts a get-together every summer at Capo Pellicano, a restaurant in the Faculty of Medicine Experimental Research Building, and a school trip every spring. These activities were well-attended and successful in 2023-24.

The OIAA oversees undergraduate clinical training (elective clerkships) for international students at the UTokyo Hospital. In 2023, 19 international students completed clinical electives of one to two months at the hospital.

1.2 Consultation regarding long-term overseas study programs for UTokyo medical students and researchers

The OIAA provides guidance and information on study abroad opportunities during the school year, prepares letters of recommendation and other documents, and supports communication with study-abroad partner institutions. Of particular importance is assisting fourth-year medical students with their elective clerkships abroad.

The Faculty of Medicine has established exchange programs that allow students to undertake clinical electives of one to two months at the University of Pennsylvania, Johns Hopkins University, the University of Michigan, the University of Hawaii, Seoul National University, National Taiwan University, National University of Singapore, Ludwig Maximilian University of Munich, and the Karolinska Institute. The OIAA also supports students who apply for electives at institutions outside of these formal agreements. Twenty medical students undertook clinical electives abroad in April–July 2023.

1.3 Support for overseas training of graduates

The OIAA prepares documents necessary for graduates applying to overseas graduate programs and those seeking medical licenses in other countries. In 2023, the office issued Medical Student Performance Evaluations (MSPEs) for graduates.

2. International Academic and Research Agreements

The OIAA maintained and renewed inter-departmental agreements with multiple partner institutions and assisted in organizing online workshops in collaboration with strategic partner universities, including the University of Chicago, National Taiwan University, and the Stockholm University Consortium. Furthermore, for the benefit of medical students from the Faculty of Medicine, a student exchange agreement for clinical electives was newly established with the Faculty of Medicine Siriraj Hospital of Mahidol University in Thailand.

3. Education and Research Activities

Dr. Florence Ene supervised and taught the Medical English I/II courses.

David Kipler conducted training for graduate and undergraduate students on academic writing and English oral presentation skills and organized workshops by distinguished guest speakers on practicing medicine in the United States and clinical decision-making.

Dr. Keiko Nanishi holds a concurrent lectureship in the School of International Health and supervised graduate students and conducted research related to international health.

Publications

- 1: Zaitzu M, Kono K, Hosokawa Y, Miyamoto M, Nanishi K, Okawa S, Niki S, Takahashi K, Yoshihara S, Kobashi G, Tabuchi T. Maternal heated tobacco product use during pregnancy and allergy in offspring. *Allergy*. 2023;78(4):1104-1112.
- 2: Toda A, Nanishi K, Shibamura A. Does benefits-of-breastfeeding language or risks-of-formula-feeding language promote more-positive attitudes toward breastfeeding among midwives and nurses? *BMC Pregnancy Childbirth*. 2023; 23(1):163.
- 3: Kikuchi K, Tuot S, Yasuoka J, Murayama M, Okawa S, Shibamura A, Nanishi K, Eng S, Huot C, Yi S. Impact of oral intervention on the oral and overall health of children living with HIV in Cambodia: a randomized controlled trial. *BMC Med*. 2023;21(1):162.
- 4: Kikuchi K, Nanishi K, Yi S, Yasuoka J. Editorial: Challenges of maternal and child health after the COVID-19 pandemic. *Front Public Health*. 2023; 11:1224093.
- 5: Nanishi K, Hongo H. Breastfeeding and the role of the commercial milk formula industry. *Lancet*. 2023;402(10400):448.
- 6: Nanishi K, Green J, Shibamura A, Hongo H, Okawa S, Tabuchi T. Challenging the utility of 24-hour recall of exclusive breast feeding in Japan. *BMJ Glob Health*. 2023;8(12):e013737.

MD Scientist Training Program

Professor and Director

Shumpei Ishikawa, M.D., Ph.D.

Assistant Professor

Yuki Sugaya, M.D., Ph.D.

Takeshi Sawada, M.D., Ph.D.

Project Assistant Professor

Yoshitaka Kurikawa, M.D., Ph.D.

Homepage <http://www.ut-mdres.umin.jp/> (in Japanese)

Introduction and Organization

The MD Scientist Training Program (MDSTP) was founded in 2008 to achieve the goal of systematically providing an intensive basic medical research training framework to the next generation of MD scientists during their MD training at the School of Medicine, The University of Tokyo. Capitalizing on the advances made by launching a reliable and sustainable program through the leadership of its first directors, Prof. Shigeo Okabe (2008-2010), Prof. Masahide Kikkawa (2011-2014), Prof. Haruhiko Bito (2015-2020), and Prof. Kenzo Hirose, the Program currently consists of its director Prof. Shumpei Ishikawa and 3 staff members, Yuki Sugaya (assistant professor), Takeshi Sawada (assistant professor) and Yoshitaka Kurikawa (project assistant professor), and over 160 students who are seeking extracurricular basic medical research training through the Program's framework. With the help of two assistants for clerical work, it provides a variety of support programs to assist the research activities of medical students. From 2011 on, the MDSTP at the University of Tokyo has cooperated with its sister programs at Kyoto University, Osaka University and Nagoya University.

The number of the enrolled students during the launch year (2008) of the MDSTP was 6. Since then, the Program has expanded and now enrolls about 160

students (during Year 3 to 6 of the Medical School). A sizable number of students write research honors theses during their final year, which they defend to become certificated as MDSTP graduates. The number of research publications in scientific journal or awards at international scientific meetings, which resulted from these theses, is growing.

Achieving basic medical research training in parallel with medical education

The Program offers a platform of activities aimed at providing an early exposure to basic medical research and to basic skills required for achieving leadership in academic medicine.

During the first 2 years after the entrance to the University of Tokyo, we initially organize a lecture series entitled 'Introduction to Medical Biology'. In this lecture series, top researchers of various fields at the University of Tokyo provide exciting but intelligible talks to students with little medical knowledge. This helps students to get introduced to various research subjects in various fields of medical research and strongly motivate them to find by themselves a laboratory suitable to their aspirations. Furthermore, we offer an opportunity to read the textbook 'Molecular Biology of the Cell' in English,

in a small group setting, to get an exposure to scientific English, and to be formally introduced to basic molecular and cellular biology, the foundation of current medical research.

From Year 3 on, as the students choose the labs and principal investigators with whom to do science with, the Program organizes journal clubs for basic medical research and courses of medical research communications are held every 2 weeks. In the journal club, students are trained to critically read recent scientific papers published in top journals, often in the presence of the first authors, if they are available. In medical research communications courses, the students discuss scientific topics and research issues with a native English speaker with a strong research background.

Students who have shown their research abilities are highly recommended to write their honors research theses by the end of the summer of Year 6. After successfully defending their theses, they are certified as qualified MDSTP trainee and, as such, they become eligible for an exemption of a part of an entrance examination for the Graduate School of Medicine. The Dean's Prize is awarded to the best thesis.

Enhancing awareness and providing opportunities for excellence in basic medical research

1) Providing assistance for research and clinical experience in foreign laboratories and hospitals

We encourage students to plan and seek for basic medical research experience in other countries during their MD training. Based on research proposals submitted to the Program, travel supports are provided on a competitive basis. In 2023, a total of 17 students received the Program's support for carrying out basic medical research abroad and to present their research achievements at international and domestic scientific meetings. We also support exposure to clinical training in foreign hospitals with the Osamu Otsubo Tetsumon Fellowship. In 2023, 11 students gained invaluable experience as student clinical clerks in various university hospitals abroad.

2) Organizing an MD scientist training program retreat

A MDSTP retreat was held on February 10 and 11, 2024 at a training facility near Tokyo to present ongoing research progress in a closed meeting among peers. More than 60 participants, mostly medical school students, but also some medical interns, graduate students and Program-affiliated professors attended it. Lively discussions among peers were exciting throughout the meeting and the feedback from all participants was outstanding and unequivocal in emphasizing the critical importance for a research progress retreat to promote their future research projects. One important aspect of the retreat was to provide students, interns, and professors to discuss opportunities in various career paths available in the basic medical research field.

3) Cooperating with other medical universities across Japan

With the availability of governmental support from 2011 to 2020, the MDSTP at the University of Tokyo has been in close touch with sister organizations at Kyoto University, Osaka University and Nagoya University. With a view to enhancing collaborative efforts in improving the basic medical research training at the 4 medical schools, joint retreats were held to promote communication and networking among the medical students with research minds. From 2021, a new partnership of the four universities, the MD Scientist Training Initiative, has been launched with the aim of working more closely together than ever before, including lab tours and research exchanges. In 2022, we held three lab tours visiting laboratories at 4 universities, with over 50 students participating in and considering study exchanges at domestic universities. The joint retreat was held in Tokyo in 2023, at the occasion of the Japan Medical Congress. More than 90 people including medical school students and teachers from all over Japan participated in this retreat and enthusiastically discussed about their research and future career as researchers.

The MSDTP also currently cooperates with 11 other universities in eastern Japan to organize annual research students' retreats. In 2023, the annual

summer retreat was held under the auspices of Tohoku University. More than 90 people participated in the retreat and presented their ongoing research progress and plans.

Activities (2022)

The number of registered students: 168 (3rd and 4th grade: 75, 5th and 6th: 93)

Lectures for students in Years 1 and 2

Introduction to Medical Biology: 13 lectures

Group reading of Molecular Biology of the Cell: 13 lectures

Seminar for students (in Year 3 or above)

Journal Club for basic medical research: 4 lectures

Medical Research Communications: 50 lectures

Presentation of research progress: 3 (the retreat of MD scientist training program in the University of Tokyo, the annual research students' retreats with universities in eastern Japan, and the MD Scientist Training Initiative joint retreat)

The number of students receiving travel supports for research: 17 (including support for international and domestic online conference)

The number of students receiving Osamu Otsubo Tetsumon Fellowship: 11

The number of Year 6 students who passed their honors thesis defense: 7 (the Dean's Prize and the Satoshi Arima memorial fellowship were awarded to 2 and 1 student, respectively)

Museum of Health and Medicine

Director

Kazuhiko Ohe

Associate

Atsushi Kitade

Homepage <https://mhm.m.u-tokyo.ac.jp/>

History and overview

The origins of the School of Medicine and the University of Tokyo Hospital can be traced back to the establishment of the Kanda Otamaga-Ike Vaccination Center in 1858. In 2008, it celebrated its 150th anniversary. The Museum of Health and Medicine was planned as part of commemorative projects to celebrate the 150th anniversary of the founding of the School and the Hospital, and was opened on January 20, 2011. One of the themes for the commemorative projects marking the 150th anniversary was the “development of communication between health science and care and society,” and the Museum of Health and Medicine forms one of the pillars of this.

In establishing the Museum of Health and Medicine, we renovated the School of Medicine’s Central Building (Medical Library), which had originally been instituted as part of the commemorative projects celebrating the 100th anniversary of the founding of the School and the Hospital. The Museum has about 400m² areas, including about 70m² of a permanent gallery and 230m² of special exhibition rooms.

The aims of the Museum are to: (1) provide health and medical information to the public, (2) educate students studying medicine, health care services and related areas, (3) research the history of medicine and health care through archives, instruments and technology, and (4) preserve and investigate valuable medical archives and instruments, etc.

In addition to the permanent gallery exhibiting accomplishments related to the School and the Hospital and its contributions made to modern and

contemporary development in Japan, a feature of the exhibitions is that a large space has also been set aside for special exhibitions to promote understanding among the public regarding the latest advances in medical science and health care. Planning and supervision of the permanent exhibition and special exhibition is done with the cooperation of the various research units within the School and the Hospital, other departments within the University, industry, and museums. Special exhibitions will be changed several times a year.

The first permanent exhibition since the opening of the Museum was a display of medical texts and instruments from the early Meiji era, an Ishihara’s Color Blind Test Chart and a gastroscope developed at the University. The first special exhibition was related to the beginnings of the School and the Hospital, Entitled “the Challenge to Infectious Diseases”. It introduced the history of vaccinations against smallpox, research into infectious diseases conducted in the University and by its graduates since the Meiji era (1868-1912), and the latest knowledge about infectious diseases. The second was “the Secret of Vessel System”, which introduced the circulatory system. The third “diagnosis of cancer”, the fourth “Our brain”, the fifth “Locomotive syndrome”, the sixth “Diabetes Mellitus”, the seventh “Pediatrics”, the eighth “Forensic Medicine”, the ninth “the Colon” followed, the tenth “Virus”, the eleventh “Kidney” and the special exhibition “Mental Diseases”.

In April 2019, we reopened our museum in the South Clinical Research Building of The University of Tokyo Hospital.

Since the opening of the Museum, more than 151,085 people had visited by the end of FY2023. Since Mar. 2020, our museum has been temporarily closed due to COVID-19 pandemic. On July 2023, We reopen. After the reopening, with the help of graduates of the School of Medicine, we launched a voice service that allows visitors to play back the exhibits in several permanent exhibitions on their smartphones. In the future, we are considering increasing the number of voices that can introducing our exhibitions and supporting foreign languages.

Overview of operations

The opening hours are 10:00-17:00. The Museum is closed every Wednesday and during the New Year holidays (however, it will open if Wednesday is a public holiday). Admission is free.

Office for Human Research Studies (OHRS)

Director of OHRS (Professor)

Masahiro Akishita, M.D., Ph.D.

Vice Director of OHRS (Associate Professor)

Yuzaburo Uetake, M.D., Ph.D.

Homepage: <http://www.m.u-tokyo.ac.jp/ethics/ethcom/gakugai2/index.html>
<http://ohrs-u-tokyo.jp>

Top page of online application system: <https://u-tokyo.bvits.com/esct/>

Introduction and Organization

The Office for Human Research Studies (OHRS) was established in October 2009 for the advancement of research ethics standards. OHRS aims to protect the rights, health, and dignity of research participants. Based on this principle, OHRS is providing research ethics support services to researchers at Graduate School of Medicine and Faculty of Medicine, the University of Tokyo and the University of Tokyo Hospital to enable them to better perform their studies in an ethical manner. Our primary task is the management of the Ethics Committee secretariat. Additionally, OHRS plans and manages research ethics seminars, provides ethics education to researchers through consultation and develops human resources for future research ethics specialists.

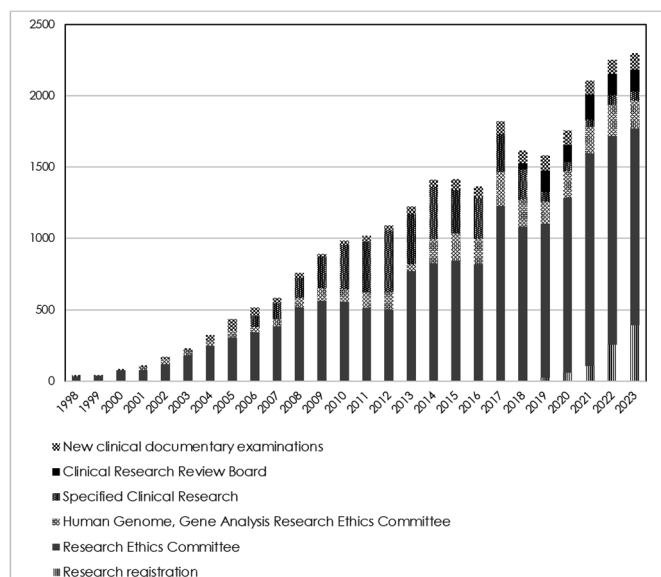
Activities

- Management of Ethics Committee
- Prior review of research activity documents (except for clinical trial, GCP), at Graduate School of Medicine and Faculty of Medicine, the University of Tokyo and the University of Tokyo Hospital. Correspond in response to various research ethics inquiries.
- Coordination of various matters with Ethics Committee members, and other similar bodies and universities.

- New clinical documentary examinations in connection with,
 - Medical treatments to implemented for the first time at the University of Tokyo Hospital,
 - Examination of the clinical use of the unapproved medicines and medical devices,
- Preparation and maintenance of the organ transplantation manuals for the liver, kidney and heart transplants.

◇ Specific items reviewed and examined by each Ethics Committee in fiscal year 2023

- Research Ethics Committee (except for clinical trial, GCP)
227 new applications, 938 minor alterations of approved studies
- Clinical Research Review Board:153
- New Clinical Documentary Examinations: 118
- Research Registration: 392



by cooperating and consulting with Ethics Consultant specified by each laboratory.

Research activities

At present, OHRS is a business section. For more information about the research, see the contents of Department of Biomedical ethics, which is a cooperative department.

Though OHRS adopts various inclusive applications, the number of studies applied to and reviewed by ethics committees over the last several years is on the increase. After the revision of the ethical guidelines, the number of institutions conducting batch reviews has increased, and the number of research registrations is also showing an upward trend.

The management duties of the Ethics Committee secretariats are complicated and diversified, making it difficult to be able provide adequate services to appropriately respond to such increasing needs.

OHRS operates an online application system and contributes to the convenience of applicants and to enable them to efficiently plan their research obligations.

Teaching and training activities

OHRS plans and manages research ethics seminars with Department of Clinical Research Governance in the University of Tokyo Hospital.

We provide a broad outline overview regarding ethics education aimed generally for all researchers and students who are engaged in clinical studies through such seminars. The ethics seminars were held monthly in fiscal year 2023 with 3322 people attended.

OHRS makes efforts to educate researchers through its research ethics support services. Additionally, the skill development and support of the secretariat staff is one of our important tasks.

OHRS also aims to advance research ethics standards

Life Sciences Core Facility (LSCF)

Professor (Director)

Masahide Kikkawa, M.D., Ph.D.

Associate Professor

Yoshihiro Kita, Ph.D.

Assistant Professor

Fumie Hamano, Ph.D.

Homepage <https://lscore.m.u-tokyo.ac.jp/>

Organization

The Life Sciences Core Facility (LSCF) was established in December 2013 to serve as a centralized hub for managing and maintaining advanced research equipment. Our mission is to provide shared access to sophisticated instruments that may be challenging for individual laboratories to procure or maintain, thereby fostering an environment that supports and enhances research activities.

The facility primarily offers equipment management and technical support for commonly utilized research instruments, catering to researchers within the Graduate School of Medicine, the School of Medicine, and the University Hospital. Key equipment under our stewardship includes cell analysis systems (cell sorters and flow cytometers), mass spectrometers (MALDI-TOFMS and LC-MS/MS), fully automated fluorescence microscopes, and large-format printers for poster preparation. These resources are integral to advancing the research efforts of our academic community.

Our support team comprises three members: a director, an associate professor, and a project assistant professor, who work collaboratively to ensure the facility operates smoothly and effectively.

Services

Equipment Maintenance and Management: We are committed to maintaining and managing a range of

research instruments to ensure their optimal performance and availability. For equipment requiring user fees, usage is tracked on a quarterly basis, and invoices are issued accordingly.

Technical Support: We provide operational support for various research instruments. For mass spectrometry systems, we also offer consultations to assist users throughout the analysis process, ensuring smooth and effective use.

Workshops and Consultations: We provide biannual training courses for the cell analysis systems, which are mandatory for accessing them. Additionally, we organize regular workshops and consultations on the fully automated fluorescence microscope to help users maximize its capabilities. To address specific needs, we have established a collaborative relationship with manufacturers, enabling us to offer a comprehensive consultation system.

Main Equipment

Cell Sorter:

- MoFlo Astrios EQs (Beckman Coulter)
 - 3-laser configuration: 1 unit
 - 5-laser configuration: 1 unit

Flow Cytometer:

- Gallios (Beckman Coulter): 1 unit

Fully Automated Fluorescence Microscope

- BZ-X710 (Keyence): 1 unit

Mass Spectrometry System

- MALDI-TOFMS: AXIMA Performance (Shimadzu): 1 unit
- Fourier Transform LC-MS: Exactive (Thermo): 1 unit

Large Format Printer (for Poster Printing)

- EPSON SC-P8050: 1 unit

The Office for Clinical Practice and Medical Education

Professor

Masato Eto, M.D., Ph.D.

Research Associate

Yuki Matsushita, M.D., Ph.D.

※The following information is the same as that of the previous year for certain reasons.

Homepage <https://igaku-kyoiku.m.u-tokyo.ac.jp/training/>

Introduction and Organization

The Office for Clinical Practice and Medical Education was established in April 2015, to support and promote medical education, especially clinical practice at grade 5 and 6. The office used to be the Clinical Clerkship Support Center, which was established to meet the change from bedside learning to clinical clerkship in February 2013. Our aim is to run the clinical clerkship (CC) smoothly, as well as to improve the curriculum and evaluation methods in cooperation with teachers and students. In addition, we try to support each student in cooperation with tutors, the instruction department and the office for student assistance in the faculty of medicine. The Information and Communication Technology (ICT) system has launched in January 2018, which greatly improved the efficiency of clerical works. The office now consists of a general manager (professor), a research associate, and three staffs.

Activities

Before the CC begins in January for 4th grade medical students, we have a meeting to explain the details to the students, and then make a schedule of the CC based on the questionnaire. Just before the CC starts, we hold a ceremony to name students that passed OSCE and CBT examinations as “student doctors”, which the dean and the chair of the academic affairs committee of the medical faculty of The University of Tokyo, and the

director and the chief nursing officer of The University of Tokyo Hospital attend.

After the CC starts, we support students, teachers and the external cooperative institutions to run the clerkship smoothly, by making necessary contacts with them. In addition, we handle with problems and considerations occurred during the practice if needed. Particularly, we manage and support students who need helps, with the instruction department, tutors, and the office for student assistance in the faculty of medicine. The new ICT system permits the evaluations of the students in the CC to be revealed real-time, hence the students are able to look their scores, at the earliest on the final day of each practice.

Twice a year, we hold a meeting with teachers who are in charge of the CC. In this meeting, we provide teachers the feedbacks about the practice from students, and exchange the information and opinions among the teachers, thus improving the CC. On the other hand, we have opportunities with students (working group on medical education), to discuss the CC and try to respond to comments from them.

Educations

Together with the IRCME department of medical education studies, we take charge of “medical practice: the introduction” for 4th grade students and “tutorial PBL” for 2th grade students, teaching medical

interview, physical examination and medical professionalism. We also take charge of tutorials and individual consultations related to the CC.

Research activities

“Research of the coherence between the students’ daily life and psychological conditions, and the outcome at the graduation” is being conducted. The results were released in the domestic and international conferences of medical education in 2018 and 2019, and published for an international paper in 2021. Presently this research is being conducted in multiple institutional investigation. Moreover, “Research of the effect of online medical interview trainings” is being conducted.

Advisory Office for Conflict of Interest

Professor

Keishi Fujio (Chair, Advisory Board for Conflict of Interest)

Professor

Kazuhiko Fukatsu (Vice Chair, Advisory Board for Conflict of Interest)

Dr. Saeko Aketani (Director, Advisory Office for Conflict of Interest)

History and Organization Overview

The Advisory Office for Conflict of Interest of the Graduate School of Medicine and University Hospital was newly established in April 2016 as an administrative department of the Advisory Board for Conflict of Interest of the School of Medicine.

At the University of Tokyo, an Advisory Board for Conflict of Interest has been established in each department under the university-wide Conflict of Interest Management Committee, and appropriate conflict of interest management is required for employees. The School of Medicine has established rules to prevent conflicts of interest in the Faculty of Medicine and has established an Advisory Board for Conflict of Interest to manage conflicts of interest in clinical research conducted at the School of Medicine and the University Hospital.

In research conducted at the School of Medicine, it is necessary to promote industry-academia collaboration activities in order to return the results to society and contribute to the health of the people. On the other hand, in clinical research involving human subjects, it is essential to protect the rights of the research subjects, and the results of the research may affect the health of the public, and the fairness of the research is particularly required. In this way, conflicts of interest are inevitable in research activities at the School of Medicine, and appropriate management and disclosure of conflicts of interest are required.

In Japan, the Ministry of Health, Labour and

Welfare (Clinical Trials Act) and the Japan Medical Association have published guidelines for managing conflicts of interest in clinical research, and the criteria for judgment are gradually being clarified, and the Advisory Office for Conflict of Interest of the School of Medicine manages conflicts of interest based on these guidelines.

Business

- The Advisory Board for Conflict of Interest at the School of Medicine manages conflicts of interest pertaining to clinical research.

Targets

- Clinical research undergoing review by the School of Medicine's Ethics Committee, encompassing studies in epidemiology, observation, intervention, and human genome and genetic analysis
- Clinical trials undergoing review by the University Hospital IRB
- Clinical research to which the Act on Securing the Safety of Regenerative Medicine, etc. applies submitted by the University Hospital
- Clinical research conducted by the University Hospital as a single center or chief facility (however, the review will be conducted by the University of Tokyo Accredited Clinical Research Review Board)
- Administrative confirmation related to self-declaration of conflicts of interest for issues to

which the Clinical Trials Act applies

- Preparation of examination materials for the management of conflicts of interest of the Japan Agency for Medical Research and Development (AMED) and the Health, Labour and Welfare Scientific Research Fund
- Task of submitting conflict of interest self-declaration forms for faculty and staff members
- Management of Conflicts of Interest of School of Medicine and University Hospital Committee Members

In FY2023, the Conflict of Interest Advisory Board consisted of six members, including external one, and conducted 11 committee meetings.

Education & Training

At the research ethics seminars hosted by the Graduate School of Medicine and the School of Medicine, the Advisory Office for Conflict of Interest manages the segment on conflict of interest in clinical research and conducts the training sessions.

Others

In July 2018, the research ethics review application system was revamped, and the operation for electronic submission of conflict of interest self-declaration forms, which were previously submitted in paper format by each researcher, was initiated on the system.

By the end of March 2019, the transition measures necessary to comply with the Clinical Research Act were completed for research projects to which the Clinical Research Act applies (part of the research projects with invasion or intervention). Furthermore, during 2018, a procedural manual for conflict of interest reviews was created for research projects to which the Clinical Research Act applies. Additionally, for projects to which the ethical guidelines for medical research involving human subjects apply, the procedural manual was revised within the same year to address the digitization of conflict of interest self-declaration forms and similar advancements. In response to the revision of the ethical guidelines during the 2021 fiscal year, we are formulating procedures for managing conflicts of interest when ethical reviews are conducted collectively by external

entities.

From April 2024 to March 2025, the Conflict of Interest Advisory Office, acting as the secretariat for the Conflict of Interest Advisory Committee, handled about 2800 new and amended applications for clinical research projects (observation, intervention, IRB, regenerative medicine safety laws, clinical research laws) in total.