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THE GRADUATE SCHOOL OF MEDICINE

AND

THE FACULTY OF MEDICINE

THE UNIVERSITY OF TOKYO

REPORTS FOR THE PERIOD April 2021 — March 2022

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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 2021-March 2022

Introduction

This is volume 145(the edition of year 2022) 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 and the Tokyo Society of Medical Sciences.

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.

Shigeo Okabe, Dean
Graduate School of Medicine and Faculty of Medicine
The University of Tokyo

October, 2022

CONTENTS

University Hospital

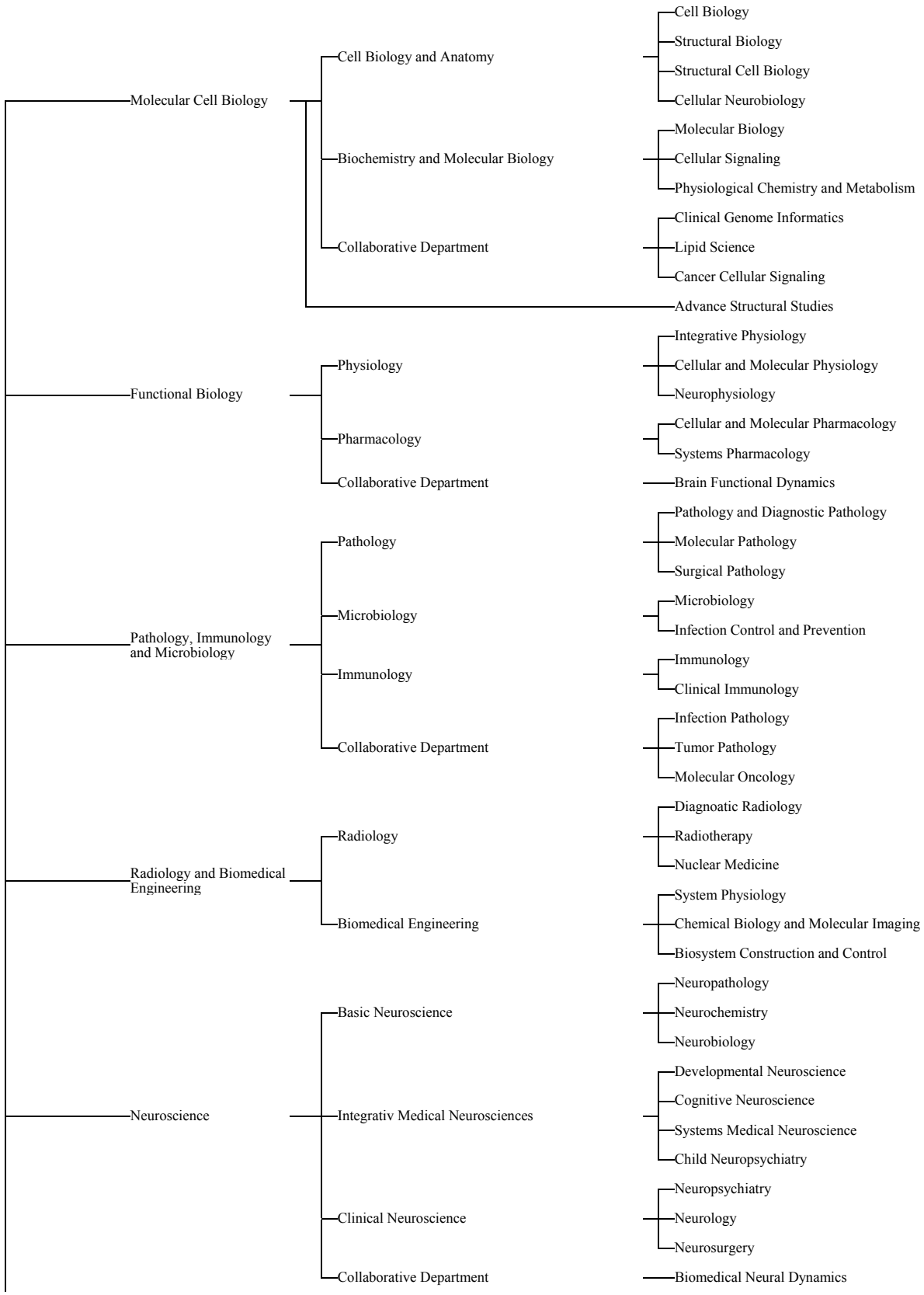
History

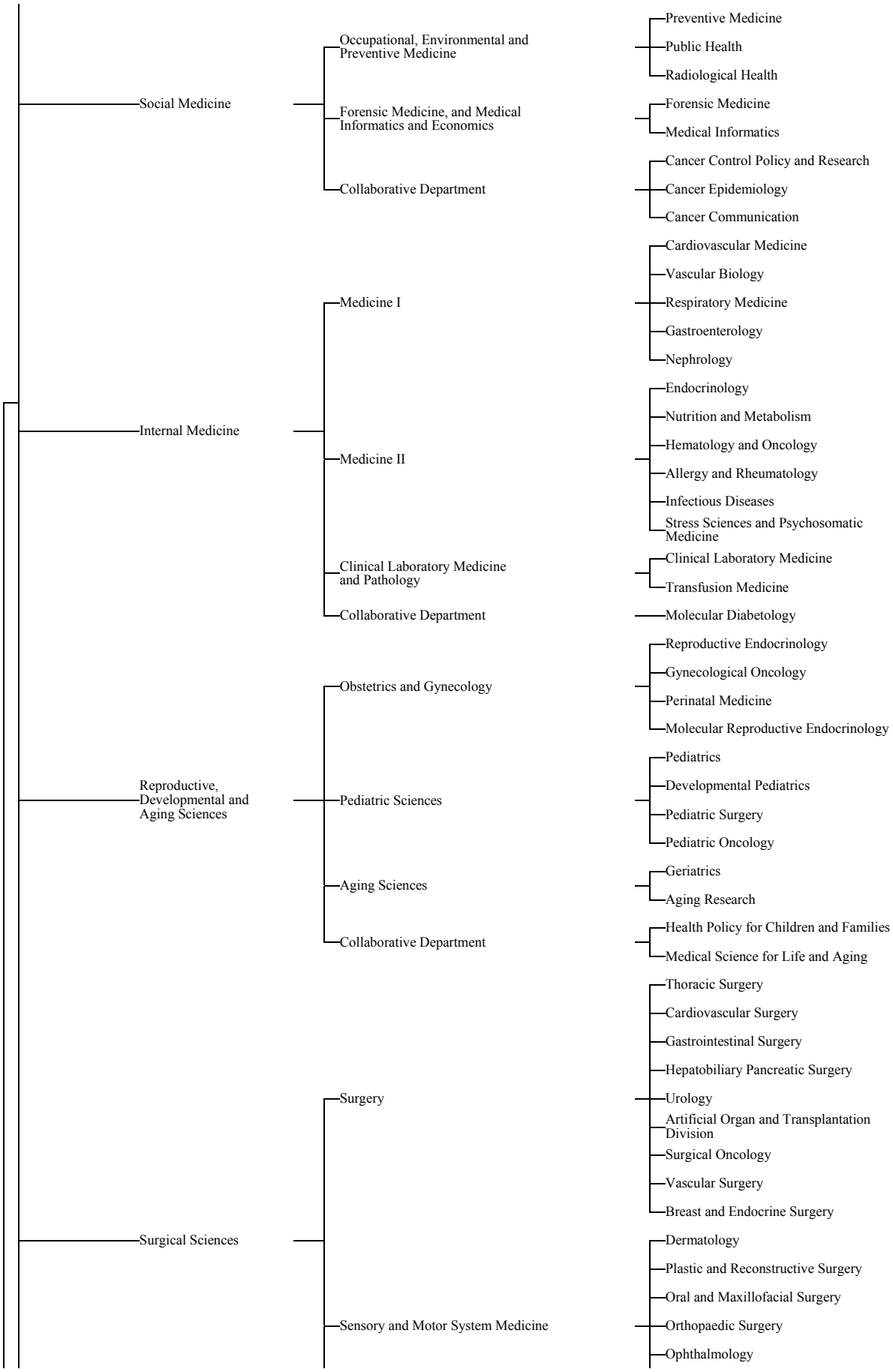
1858	May	Practitioners, trained in Dutch (European) medicine in Edo (Tokyo), laid out money to establish the Shutojo (vaccination center) in Kanda Mitamagaike.
	Nov.	Shutojo was destroyed in a fire that had spread from Kanda Aioicho. Shutojo continued its operations at other sites such as the residence 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	Oct.	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.

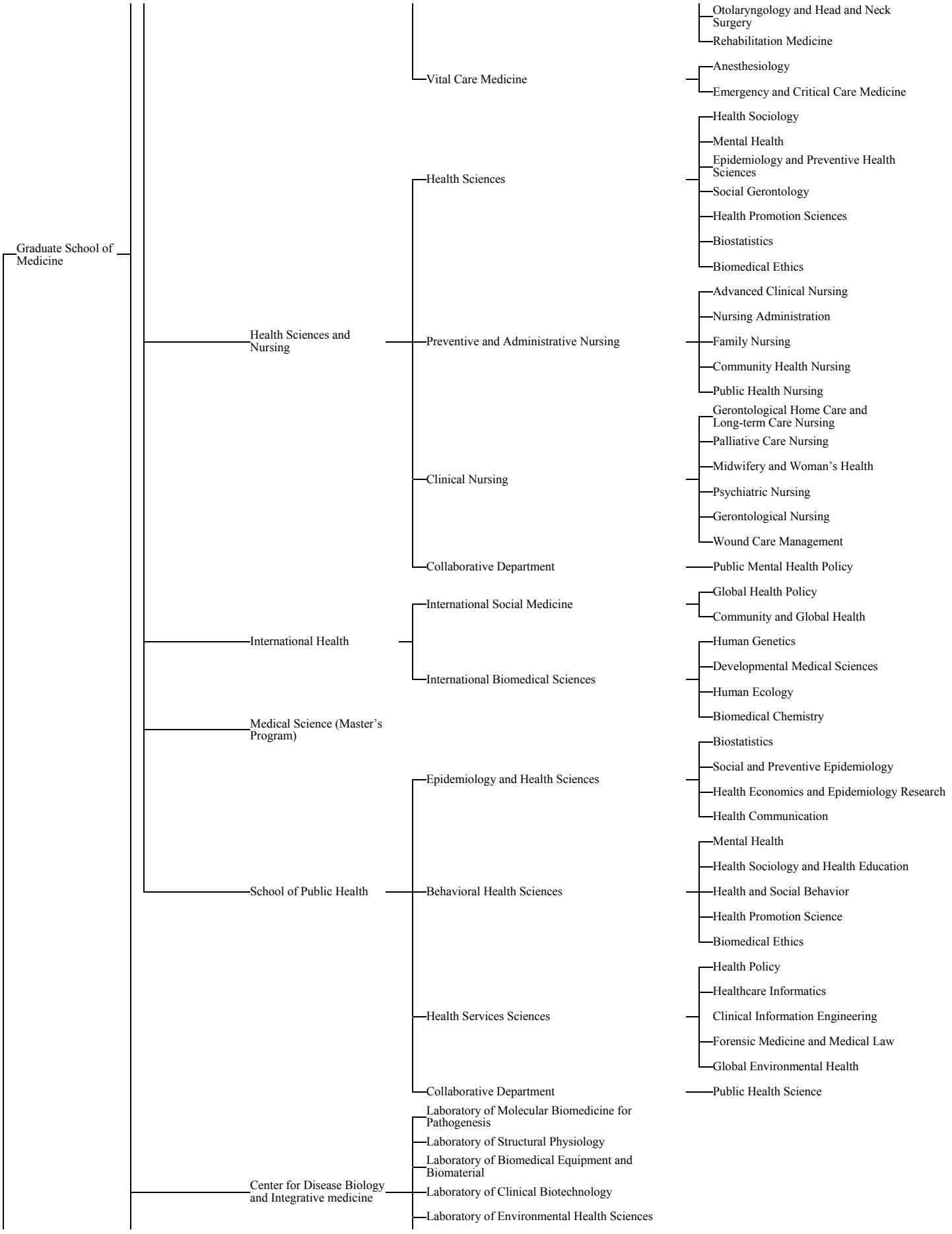
	Jul.	The Graduate School was founded, and the Division of Medical Doctor Biological Science was established. The Brain Research Laboratory became the Brain Research Institute of the Faculty of Medicine.
1956	Apr.	The Midwives School was established.
1958	Apr.	The Division of Pharmaceutical Sciences became an independent faculty.
	May	The University of Tokyo Faculty of Medicine celebrated its centennial anniversary.
1961	Mar.	The Medical Library was built in commemoration of the centenary.
	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	Sep.	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 Master course of Medical Science 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.

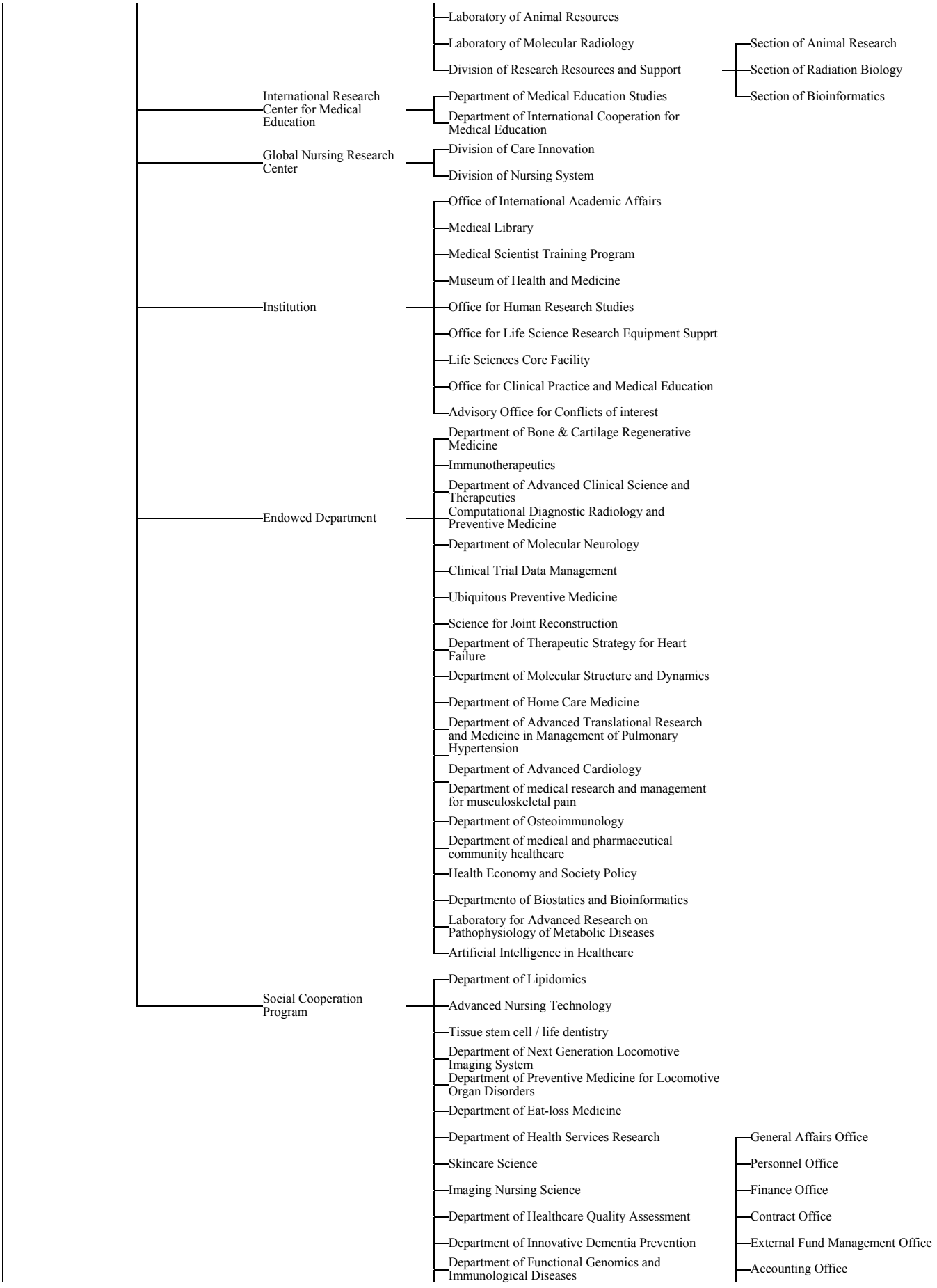
2000	Apr.	The International Research Center for Medical Education was established (A shared facility for education and research).
2001	Apr.	The University Branch Hospital was united with the University Hospital.
2002	Mar.	Nursing School and Midwives School was Closed.
2002	Mar.	Experimental Building (First Stage) was constructed.
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.
2013	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.
2017	Apr.	The Institute for Life Science Research and Education was established.
2017	Apr.	The Research Institute for Biomedical Science and Engineering 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.

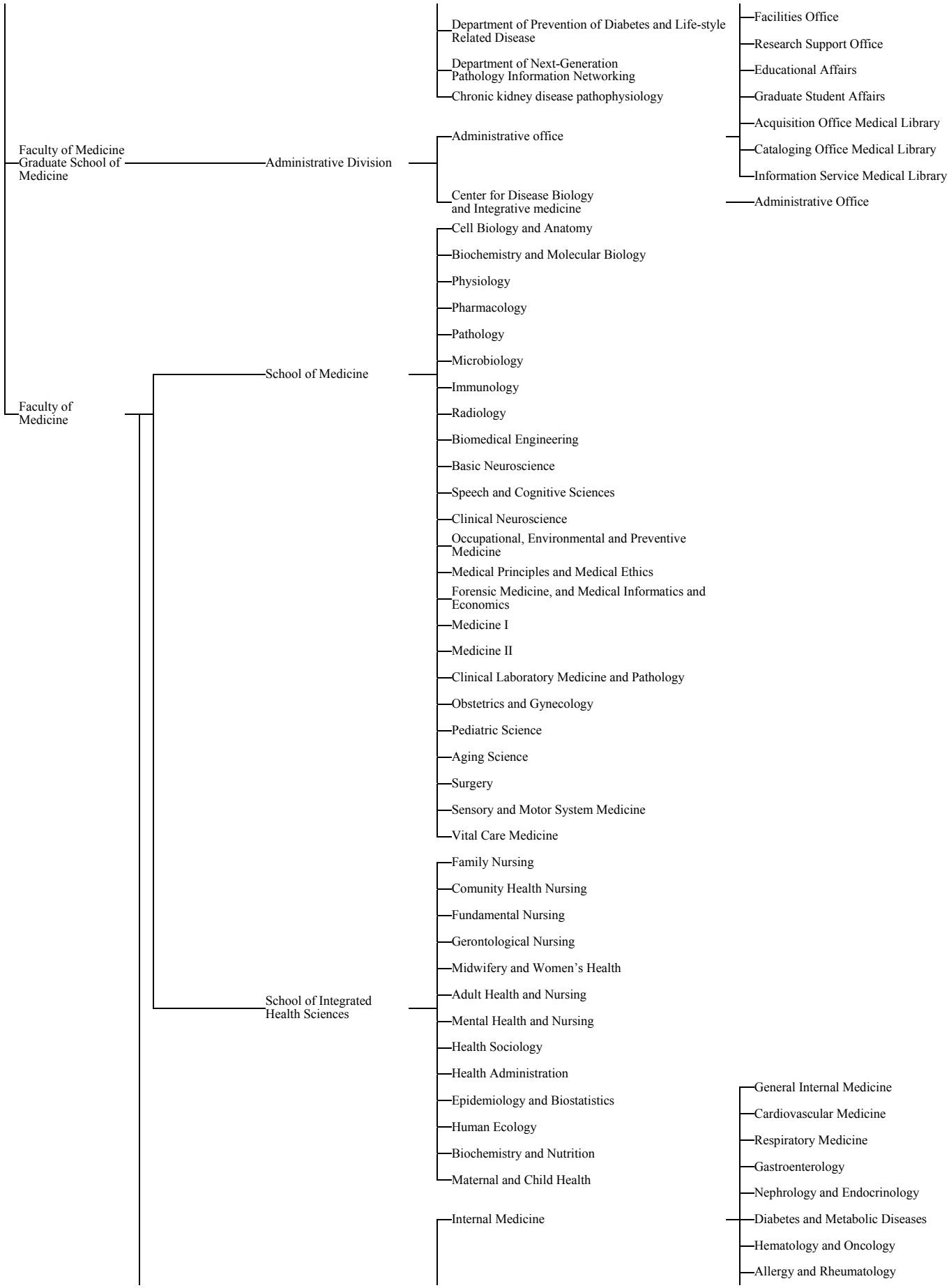
Organization Chart

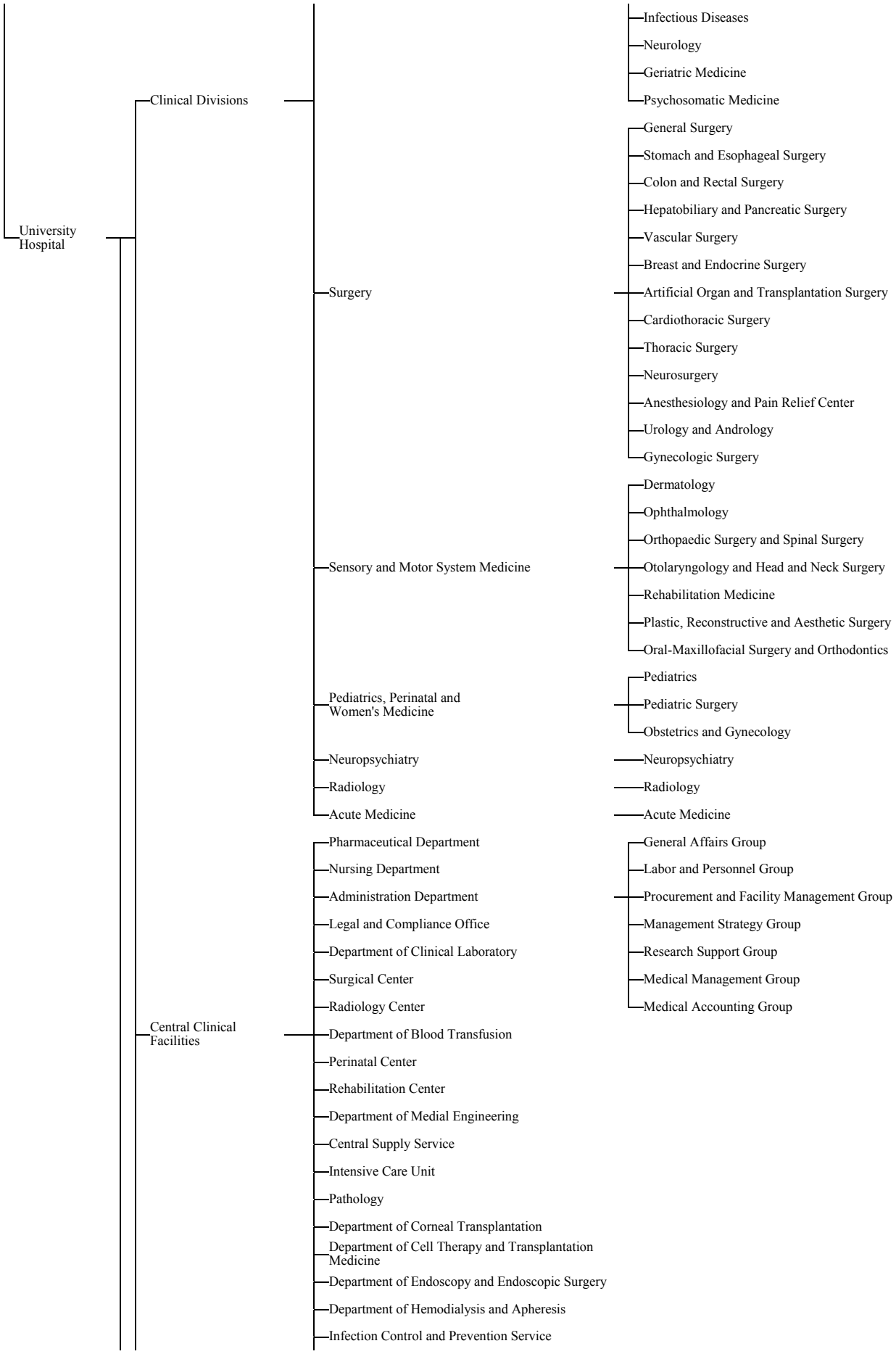


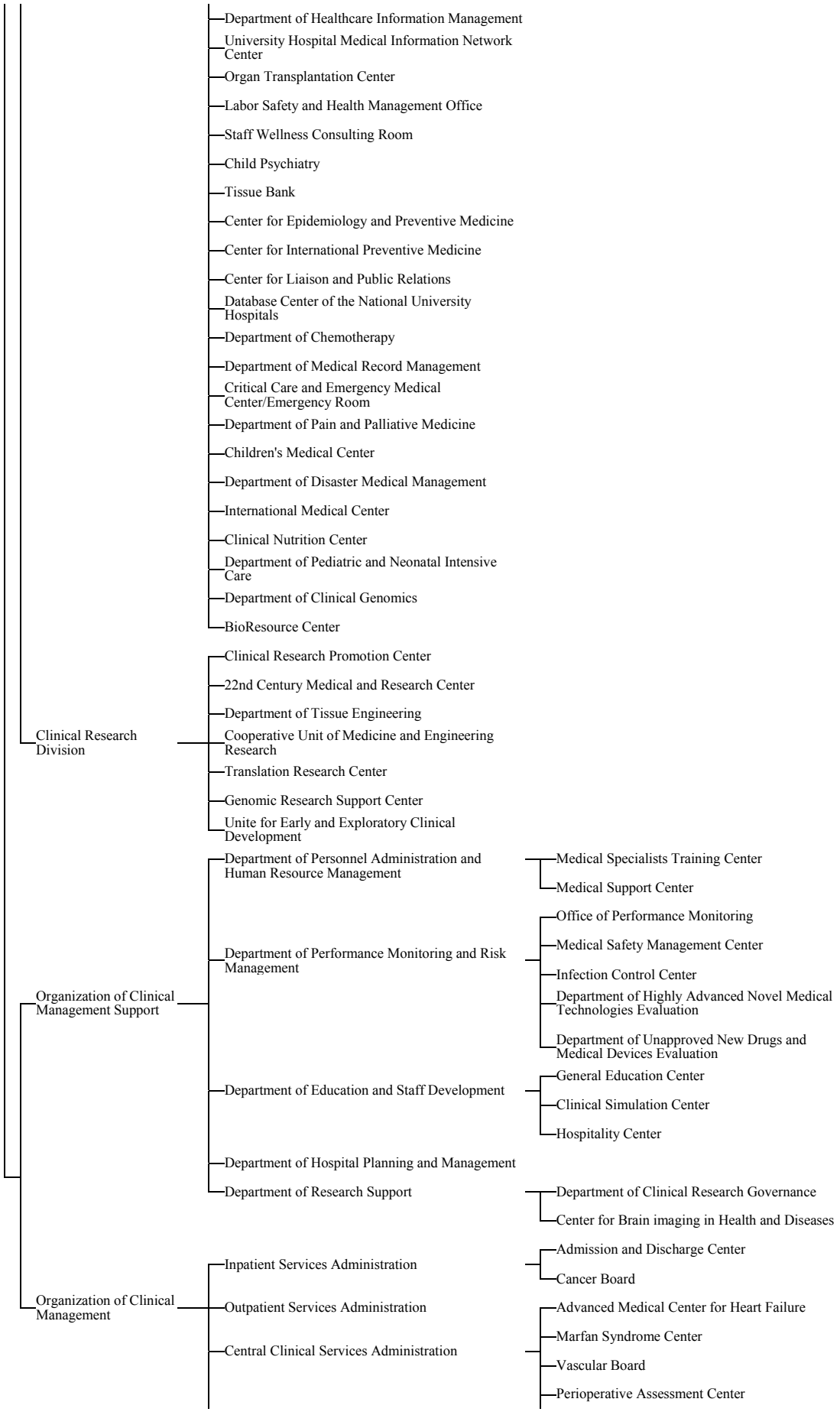

Social Medicine
Occupational, Environmental and Preventive Medicine
Preventive Medicine
Public Health
Radiological Health
Forensic Medicine, and Medical Informatics and Economics
Forensic Medicine
Medical Informatics
Collaborative Department
Cancer Control Policy and Research
Cancer Epidemiology
Cancer Communication
Internal Medicine
Medicine I
Cardiovascular Medicine
Vascular Biology
Respiratory Medicine
Gastroenterology
Nephrology
Medicine II
Endocrinology
Nutrition and Metabolism
Hematology and Oncology
Allergy and Rheumatology
Infectious Diseases
Stress Sciences and Psychosomatic Medicine
Clinical Laboratory Medicine and Pathology
Clinical Laboratory Medicine
Transfusion Medicine
Collaborative Department
Molecular Diabetology
Reproductive, Developmental and Aging Sciences
Obstetrics and Gynecology
Reproductive Endocrinology
Gynecological Oncology
Perinatal Medicine
Molecular Reproductive Endocrinology
Pediatric Sciences
Pediatrics
Developmental Pediatrics
Pediatric Surgery
Pediatric Oncology
Aging Sciences
Geriatrics
Aging Research
Collaborative Department
Health Policy for Children and Families
Medical Science for Life and Aging
Surgical Sciences
Surgery
Thoracic Surgery
Cardiovascular Surgery
Gastrointestinal Surgery
Hepatobiliary Pancreatic Surgery
Urology
Artificial Organ and Transplantation Division
Surgical Oncology
Vascular Surgery
Breast and Endocrine Surgery
Sensory and Motor System Medicine
Dermatology
Plastic and Reconstructive Surgery
Oral and Maxillofacial Surgery
Orthopaedic Surgery
Ophthalmology

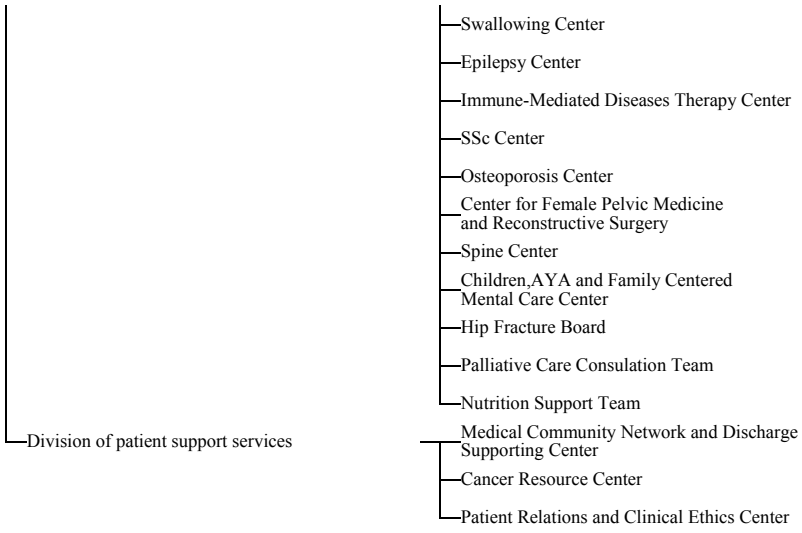

Graduate School of Medicine
Health Sciences and Nursing
Health Sciences
Otolaryngology and Head and Neck Surgery
Rehabilitation Medicine
Vital Care Medicine
Anesthesiology
Emergency and Critical Care Medicine
Health Sociology
Mental Health
Epidemiology and Preventive Health Sciences
Social Gerontology
Health Promotion Sciences
Biostatistics
Biomedical Ethics
Preventive and Administrative Nursing
Advanced Clinical Nursing
Nursing Administration
Family Nursing
Community Health Nursing
Public Health Nursing
Clinical Nursing
Gerontological Home Care and Long-term Care Nursing
Palliative Care Nursing
Midwifery and Woman's Health
Psychiatric Nursing
Gerontological Nursing
Wound Care Management
Collaborative Department
Public Mental Health Policy
International Health
International Social Medicine
Global Health Policy
Community and Global Health
International Biomedical Sciences
Human Genetics
Developmental Medical Sciences
Human Ecology
Biomedical Chemistry
Medical Science (Master's Program)
School of Public Health
Epidemiology and Health Sciences
Biostatistics
Social and Preventive Epidemiology
Health Economics and Epidemiology Research
Health Communication
Behavioral Health Sciences
Mental Health
Health Sociology and Health Education
Health and Social Behavior
Health Promotion Science
Biomedical Ethics
Health Services Sciences
Health Policy
Healthcare Informatics
Clinical Information Engineering
Forensic Medicine and Medical Law
Global Environmental Health
Collaborative Department
Public Health Science
Center for Disease Biology and Integrative medicine
Laboratory of Molecular Biomedicine for Pathogenesis
Laboratory of Structural Physiology
Laboratory of Biomedical Equipment and Biomaterial
Laboratory of Clinical Biotechnology
Laboratory of Environmental Health Sciences


Laboratory of Animal Resources
Laboratory of Molecular Radiology
Division of Research Resources and Support
Section of Animal Research
Section of Radiation Biology
Section of Bioinformatics
International Research Center for Medical Education
Department of Medical Education Studies
Department of International Cooperation for Medical Education
Global Nursing Research Center
Division of Care Innovation
Division of Nursing System
Institution
Office of International Academic Affairs
Medical Library
Medical Scientist Training Program
Museum of Health and Medicine
Office for Human Research Studies
Office for Life Science Research Equipment Supprt
Life Sciences Core Facility
Office for Clinical Practice and Medical Education
Advisory Office for Conflicts of interest
Endowed Department
Department of Bone & Cartilage Regenerative Medicine
Immunotherapeutics
Department of Advanced Clinical Science and Therapeutics
Computational Diagnostic Radiology and Preventive Medicine
Department of Molecular Neurology
Clinical Trial Data Management
Ubiquitous Preventive Medicine
Science for Joint Reconstruction
Department of Therapeutic Strategy for Heart Failure
Department of Molecular Structure and Dynamics
Department of Home Care Medicine
Department of Advanced Translational Research and Medicine in Management of Pulmonary Hypertension
Department of Advanced Cardiology
Department of medical research and management for musculoskeletal pain
Department of Osteoimmunology
Department of medical and pharmaceutical community healthcare
Health Economy and Society Policy
Departmento of Biostatics and Bioinformatics
Laboratory for Advanced Research on Pathophysiology of Metabolic Diseases
Artificial Intelligence in Healthcare
Social Cooperation Program
Department of Lipidomics
Advanced Nursing Technology
Tissue stem cell / life dentistry
Department of Next Generation Locomotive Imaging System
Department of Preventive Medicine for Locomotive Organ Disorders
Department of Eat-loss Medicine
Department of Health Services Research
Skincare Science
Imaging Nursing Science
Department of Healthcare Quality Assessment
Department of Innovative Dementia Prevention
Department of Functional Genomics and Immunological Diseases
General Affairs Office
Personnel Office
Finance Office
Contract Office
External Fund Management Office
Accounting Office


Faculty of Medicine Graduate School of Medicine
Administrative Division
Administrative office
Facilities Office
Research Support Office
Educational Affairs
Graduate Student Affairs
Acquisition Office Medical Library
Cataloging Office Medical Library
Information Service Medical Library
Center for Disease Biology and Integrative medicine
Administrative Office
Department of Prevention of Diabetes and Life-style Related Disease
Department of Next-Generation Pathology Information Networking
Chronic kidney disease pathophysiology
Faculty of Medicine
School of Medicine
Cell Biology and Anatomy
Biochemistry and Molecular Biology
Physiology
Pharmacology
Pathology
Microbiology
Immunology
Radiology
Biomedical Engineering
Basic Neuroscience
Speech and Cognitive Sciences
Clinical Neuroscience
Occupational, Environmental and Preventive Medicine
Medical Principles and Medical Ethics
Forensic Medicine, and Medical Informatics and Economics
Medicine I
Medicine II
Clinical Laboratory Medicine and Pathology
Obstetrics and Gynecology
Pediatric Science
Aging Science
Surgery
Sensory and Motor System Medicine
Vital Care Medicine
School of Integrated Health Sciences
Family Nursing
Comunity Health Nursing
Fundamental Nursing
Gerontological Nursing
Midwifery and Women's Health
Adult Health and Nursing
Mental Health and Nursing
Health Sociology
Health Administration
Epidemiology and Biostatistics
Human Ecology
Biochemistry and Nutrition
Maternal and Child Health
Internal Medicine
General Internal Medicine
Cardiovascular Medicine
Respiratory Medicine
Gastroenterology
Nephrology and Endocrinology
Diabetes and Metabolic Diseases
Hematology and Oncology
Allergy and Rheumatology


University Hospital
Clinical Divisions
Surgery
Infectious Diseases
Neurology
Geriatric Medicine
Psychosomatic Medicine
General Surgery
Stomach and Esophageal Surgery
Colon and Rectal Surgery
Hepatobiliary and Pancreatic Surgery
Vascular Surgery
Breast and Endocrine Surgery
Artificial Organ and Transplantation Surgery
Cardiothoracic Surgery
Thoracic Surgery
Neurosurgery
Anesthesiology and Pain Relief Center
Urology and Andrology
Gynecologic Surgery
Sensory and Motor System Medicine
Dermatology
Ophthalmology
Orthopaedic Surgery and Spinal Surgery
Otolaryngology and Head and Neck Surgery
Rehabilitation Medicine
Plastic, Reconstructive and Aesthetic Surgery
Oral-Maxillofacial Surgery and Orthodontics
Pediatrics, Perinatal and Women's Medicine
Pediatrics
Pediatric Surgery
Obstetrics and Gynecology
Neuropsychiatry
Neuropsychiatry
Radiology
Radiology
Acute Medicine
Acute Medicine
Central Clinical Facilities
Pharmaceutical Department
Nursing Department
Administration Department
Legal and Compliance Office
Department of Clinical Laboratory
Surgical Center
Radiology Center
Department of Blood Transfusion
Perinatal Center
Rehabilitation Center
Department of Medial Engineering
Central Supply Service
Intensive Care Unit
Pathology
Department of Corneal Transplantation
Department of Cell Therapy and Transplantation Medicine
Department of Endoscopy and Endoscopic Surgery
Department of Hemodialysis and Apheresis
Infection Control and Prevention Service
General Affairs Group
Labor and Personnel Group
Procurement and Facility Management Group
Management Strategy Group
Research Support Group
Medical Management Group
Medical Accounting Group


Department of Healthcare Information Management
University Hospital Medical Information Network Center
Organ Transplantation Center
Labor Safety and Health Management Office
Staff Wellness Consulting Room
Child Psychiatry
Tissue Bank
Center for Epidemiology and Preventive Medicine
Center for International Preventive Medicine
Center for Liaison and Public Relations
Database Center of the National University Hospitals
Department of Chemotherapy
Department of Medical Record Management
Critical Care and Emergency Medical Center/Emergency Room
Department of Pain and Palliative Medicine
Children's Medical Center
Department of Disaster Medical Management
International Medical Center
Clinical Nutrition Center
Department of Pediatric and Neonatal Intensive Care
Department of Clinical Genomics
BioResource Center
Clinical Research Division
Clinical Research Promotion Center
22nd Century Medical and Research Center
Department of Tissue Engineering
Cooperative Unit of Medicine and Engineering Research
Translation Research Center
Genomic Research Support Center
Unite for Early and Exploratory Clinical Development
Organization of Clinical Management Support
Department of Personnel Administration and Human Resource Management
Medical Specialists Training Center
Medical Support Center
Department of Performance Monitoring and Risk Management
Office of Performance Monitoring
Medical Safety Management Center
Infection Control Center
Department of Highly Advanced Novel Medical Technologies Evaluation
Department of Unapproved New Drugs and Medical Devices Evaluation
Department of Education and Staff Development
General Education Center
Clinical Simulation Center
Hospitality Center
Department of Hospital Planning and Management
Department of Research Support
Department of Clinical Research Governance
Center for Brain imaging in Health and Diseases
Organization of Clinical Management
Inpatient Services Administration
Admission and Discharge Center
Cancer Board
Outpatient Services Administration
Central Clinical Services Administration
Advanced Medical Center for Heart Failure
Marfan Syndrome Center
Vascular Board
Perioperative Assessment Center


Swallowing Center
Epilepsy Center
Immune-Mediated Diseases Therapy Center
SSc Center
Osteoporosis Center
Center for Female Pelvic Medicine and Reconstructive Surgery
Spine Center
Children,AYA and Family Centered Mental Care Center
Hip Fracture Board
Palliative Care Consulation Team
Nutrition Support Team
Division of patient support services
Medical Community Network and Discharge Supporting Center
Cancer Resource Center
Patient Relations and Clinical Ethics Center

Teaching, Research, Secretarial and Administrative Staffs

Chief Members of Administration

Dean, Graduate School of Medicine	Shigeo Okabe
(Dean, Faculty of Medicine)	
Chairman, School of Health Sciences and Nursing	Masahiro Umezaki
Director, Medical Library	Hideo Yasunaga
Director General, University Hospital	Yasuyuki Seto
Director, Center for Disease Biology and Integrative Medicine	Masanobu Kano
Director, International Research Center for Medical Education	Tatsuya Yamasoba
Director, Global Nursing Research Center	Hiromi Sanada

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	Makoto Murakami
	Professor	Hiroki Kurihara
	Professor	Radostin Stoyanov Danev

Functional Biology

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

Pathology, Immunology and Microbiology

Department of Pathology	Professor	Tetsuo Ushiku
	Professor	Kohei Miyazono
Department of Microbiology	Professor	Masanori Hatakeyama
	Professor	Kyoji Moriya
Department of Immunology	Professor	Hiroshi Takayanagi

Radiology and Biomedical Engineering

Department of Radiology	Professor	Osamu Abe

Department of Biomedical Engineering	Professor	Kiyoshi Miyagawa
	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	Yasuki Kobayashi
Department of Forensic Medicine, and Medical Informatics and Economics	Professor	Hirotaro Iwase
	Professor	Kazuhiko Ohe
Internal Medicine		
Department of Medicine I	Professor	Issei Komuro
	Professor	Takahide Nagase
	Professor	Mitsuhiro Fujishiro
Department of Medicine II	Professor	Masaomi Nangaku
	Professor	Toshimasa Yamauchi
	Professor	Mineo Kurokawa
	Professor	Keishi Fujio
	Professor	Kyoji Moriya
Department of Clinical Laboratory Medicine and Pathology	Professor	Yutaka Yatomi
	Professor	Hitoshi Okazaki
Reproductive, Developmental and Aging Science		
Department of Obstetrics and Gynecology	Professor	Yutaka Osuga
Department of Pediatric Science	Professor	Motohiro Kato
	Professor	Jun Fujishiro
Department of Aging Science	Professor	Masahiro Akishita
Surgical Sciences		
Department of Surgery	Professor	Jun Nakajima
	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	Tatsuya Yamasoba
	Professor	Toru Ogata
Department of Vital Care Medicine	Professor	Kanji Uchida
	Professor	Kento Doi
Health Sciences and Nursing		
Department of Health Sciences	Professor	Norito Kawakami
	Professor	Yutaka Matsuyama
	Professor	Hideki Hashimoto
	Professor	Akira Akabayashi
Department of Preventive and Administrative Nursing	Professor	Mari Ikeda
	Professor	Noriko Yamamoto
Department of Clinical Nursing	Professor	Noriko Yamamoto
	Professor	Megumi Haruna
	Professor	Norito Kawakami
	Professor	Hiromi Sanada
International Health		
Department of International Social Medicine	Professor	Masahiro Hashizume
	Professor	Masamine Jinba
Department of International Biomedical Sciences	Professor	Akihiro Fujimoto
	Professor	Moi Meng Ling
	Professor	Masahiro Umezaki
	Professor	Tomoyoshi Nozaki
School of Public Health		
Department of Epidemiology and Health Sciences	Professor	Yutaka Matsuyama
	Professor	Satoshi Sasaki
	Professor	Hideo Yasunaga
	Professor	Takahiro Kiuchi
Department of Behavioral Health Sciences	Professor	Norito Kawakami
	Professor	Hideki Hashimoto
	Professor	Akira Akabayashi
Department of Health Services Sciences	Professor	Yasuki Kobayashi
	Professor	Kazuhiko Ohe
	Professor	Hiroshi Oyama
	Professor	Hirotaro Iwase

Center for Disease Biology and Integrative Medicine		
Laboratory of Molecular Biomedicine for Pathogenesis	Professor	Toru Miyazaki
Laboratory of Structural Physiology	Professor	Haruo Kasai
Division of Biomedical Equipment and Biomaterials	Professor	Taichi Ito
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	Professor	Kiyoshi Miyagawa
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	Kenzo Hirose
Museum of Health and Medicine	Professor	Kazuhiko Ohe
Office for Human Research Studies	Professor	Masaomi Nangaku
Life Sciences Core Facility	Associate Professor	Yoshihiro Kita
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 in Healthcare	Project Associate professor	Yoshimasa Kawazoe
Department of Bone & Cartilage Regenerative Medicine	Project Associate professor	Atsuhiko Hikita
Department of Immunotherapeutics	Project Professor	Kazuhiro Kakimi
Department of Advanced Clinical Science and Therapeutics	Project Associate professor	Mutsuo Harada
Computational Diagnostic Radiology and Preventive Medicine	Project Professor	Naoto Hayashi
Science for Joint Reconstruction	Project professor	Toru Moro
Therapeutic Strategy for Heart Failure	Project Associate professor	Eisuke Amiya
Department of Molecular Structure and Dynamics		
Department of Advanced Translational Research and	Project Associate professor	Yuichi Ikeda
Medical research and Management for Musculoskeletal pain	Project Professor	Koh Matsudaira
Department of Osteoimmunology	Project Associate professor	Kazuo Okamoto
Department of medical and pharmaceutical community healthcare	Project Professor	Hirohisa Imai
Department of Healthcare economics and Health policy	Project Professor	Tomoyuki Takura
Department of Biostatistics and Bioinformatics	Project Professor	Daisuke Koide

Department of Molecular Neurology	Project Professor	Syoji Tsuji
Laboratory for Advanced Research on Pathophysiology of Metabolic Diseases	Project Associate Professor	Miki Iwabu
Department of Home Care Medicine	Project Associate Professor	Takashi Yamanaka
Department of Advanced Cardiology	Project Associate Professor	Katsuhito Fujiu
Clinical Trial Data Management		
Research on Cell Therapy of Regenerative Medicine	Project Associate Professor	Dehua Chang
Comprehensive radiation oncology	Project Professor	Keiichi Nakagawa

Social Cooperation Program

Department of Lipidomics	Project Professor	Yoshiya Oda
Advanced Nursing Technology	Project Associate professor	Ryoko Murayama
Department of Health Services Research	Project Associate professor	Taisuke Jo
Skincare Science	Project Associate professor	Takeo Minematsu
Imaging Nursing Science	Project Associate professor	Nao Tamai
Healthcare Quality Assessment	Project Professor	Hiroaki Miyata
Department of Innovative Dementia Prevention	Project Associate professor	Tomoko Wakabayashi
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
Chronic Kidney Disease Pathophysiology	Project Professor	Reiko Inagi
Department of Functional Genomics and Immunological Diseases	Project Associate professor	Tomohisa Okamura
Tissue stem cell / life dentistry	Project Professor	Makoto Komura
Department of Next Generation Locomotive Imaging System	Project Associate professor	Yuki Taniguchi
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	Hidenori Kage
Department of Pain & Palliative Medical Sciences	Project Associate professor	Maiko Hasegawa
Department of Retinal Biology and Pathology	Project Professor	Sumiko Watanabe
Medical information engineering	Project Associate professor	Taichi Kin

University Hospital

Clinical Divisions

General Internal Medicine	Head	Masahiro Akishita
Cardiovascular Medicine	Head	Issei Komuro
Respiratory Medicine	Head	Takahide Nagase
Gastroenterology	Head	Mitsuhiro Hujishiro
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	Kyoji Moriya
Neurology	Head	Tatsushi Toda
Geriatric Medicine	Head	Masahiro Akishita
Psychosomatic Medicine	Head	Kazuhiro Yoshiuchi
General Surgery	Head	Soichiro Ishihara
Stomach and Esophagus Surgery	Head	Yasuyuki Seto
Colon and Rectal Surgery	Head	Soichiro Ishihara
Hepatobiliary 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	Jun Nakajima
Neurosurgery	Head	Nobuhito Saito
Anesthesiology and Pain Relief Center	Head	Kanji Uchida
Urology and Andrology	Head	Haruki Kume
Gynecologic Surgery	Head	Yutaka Ohsuga
Dermatology	Head	Shinichi Sato
Ophthalmology	Head	Makoto Aihara
Orthopaedic Surgery and Spinal Surgery	Head	Sakae Tanaka
Otorhinolaryngology and Head and Neck Surgery	Head	Tatsuya Yamasoba
Rehabilitation Medicine	Head	Toru Ogata
Plastic, Reconstructive and Aesthetic Surgery	Head	Mutsumi Okazaki
Oral-Maxillofacial Surgery and Orthodontics	Head	Kazuto Hoshi
Pediatrics	Head	Motohiro Kato
Pediatric Surgery	Head	Jun Fujishiro
Obstetrics and Gynecology	Head	Yutaka Ohsuga
Neuropsychiatry	Head	Kiyoto Kasai
Radiology	Head	Osamu Abe

Acute Medicine	Head	Kento Doi
Central Clinical Facilites		
Pharmaceutical Department	Head	Hiroshi Suzuki
Department of Clinical Laboratory	Head	Yutaka Yatomi
Surgical Center	Head	Kazuhiko Fukatsu
Radiology Center	Head	Osamu Abe
Department of Blood Transfusion	Head	Hitoshi Okazaki
Perinatal Center	Head	Yutaka Ohsuga
Rehabilitation Center	Head	Toru Ogata
Department of Medical Engineering	Head	Kento Doi
Central Supply Service	Head	Kazuhiko Fukatsu
Intensive Care Unit	Head	Kento Doi
Pathology	Head	Tetsuo Ushiku
Department of Corneal Transplantation	Head	Makoto Aihara
Department of Cell Therapy and Transplantation Medicine	Head	Mineo Kurokawa
Department of Endoscopy and Endoscopic Surgery	Head	Yousuke Nakai
Department of Hemodialysis and Apheresis	Head	Masaomi Nangaku
Infection Control and Prevention Service	Head	Kyoji Moriya
Department of Healthcare Information Management	Head	Kazuhiko Ohe
University Hospital Medical Information Network Center	Head	Takahiro Kiuchi
Organ Transplantation Service	Head	Jun Nakajima
Labor Safety and Health Management Office	Head	Tomotaka Yamamoto
Child Psychiatry	Head	Yukiko Kano
Tissue Bank	Head	Sumihito Tamura
Epidemiology and Preventive Medicine	Head	Nobutake Yamamichi
Center for Liaison and Public Relations	Head	Yutaka Osuga
Department of Chemotherapy	Head	Kiyoshi Miyagawa
Department of Medical Record Management	Head	Kazuhiko Ohe
Critical Care and Emergency Medical Center/ER	Head	Kento Doi
Department of Pain and Palliative Medicine	Head	Masahiko Sumitani
Children’s Medical Center	Head	Naoto Takahashi
Department of Disaster Medical Management	Head	Kento Doi
International Medical Center	Head	Sumihito Tamura
Department of Clinical Nutrition Therapy	Head	Naoto Kubota
Department of Pediatric and Neonatal Intensive Care	Head	Naoto Takahashi
Department of Clinical Genomics	Head	Katsutoshi Oda
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	Issei Komuro
Genomic Research Support Center	Head	Yutaka Osuga
Unit for Early and Exploratory Clinical Development	Head	Takeshi Iwatsubo

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

Daisuke Takao, 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), Daisuke Takao (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. Aoyama-Ishiwatari S, Okazaki T, Iemura S, Natsume T, Okada Y, Gotoh T. NUDT21 links mitochondrial IPS-1 to RLR-containing stress granules and activates host antiviral defense. The

Journal of Immunology 206 (1), 154-163, 2021

2. Nakamura TS, Suda Y, Muneshige K, Fujieda Y, Okumura Y, Inoue I, Tanaka T, Takahashi T, Nakanishi H, Gao XD, Okada Y, Neiman AM, Tachikawa H. Suppression of Vps13 adaptor protein mutants reveals a central role for PI4P in regulating prospore membrane extension. PLoS Genet 17(8): e1009727. 2021
3. Kowada R, Kodani A, Ida H, Yamaguchi M, Lee IS, Okada Y, Yoshida H. The function of Scox in glial cells is essential for locomotive ability in Drosophila. Sci Rep. 11:21207. 2021
4. Ishijima A, Okada Y. Information biophysics of gradient sensing in organisms. Biophys Physicobiol. 18:263-264. 2021
5. Yaginuma H, Okada Y. Live cell imaging of metabolic heterogeneity by quantitative fluorescent ATP indicator protein, QUEEN-37C. bioRxiv: 2021.10.08.463131. 2021
6. Yoshida S, Okada Y, Muneyuki E, Ito S. Thermodynamic role of main reaction pathway and multi-body information flow in membrane transport. arXiv:2112.04024, 2021 (published in Phys Rev Res 4, 023229, 2022).

Department of Cell Biology & Anatomy (Structural Biology)

Professor

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

Lecturer

Haruaki Yanagisawa, Ph.D.

Project Lecturer

Yoshiyuki Fukuda, 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), Akihisa Tsutsumi (project research associate), (project researcher), Ryohei Sasaki, Jiancheng An, Yuma Tani, and Yuqing Liu (graduate students), Ueno Risa and Takemasa Saguchi (MSTP students), Akiko Oosakaya, Sakamaki Yoichi, and Toshie Furuya (technical assistant), Kazuhiro Nakamura (Advanced Academic Specialist), and Mikako Yanagiuchi and Setsuko Yuge (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 eukaryotic flagella/cilia. Flagella/cilia is both “propeller” and “antenna” of cells, whose diameter is about 250 nm. From the 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 strength is in the 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 macromolecular 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. T. Kobayashi, A. Tsutsumi, N. Kurebayashi, K. Saito, M. Kodama, T. Sakurai, **M. Kikkawa**, T. Murayama, and H. Ogawa. Molecular basis for gating of cardiac ryanodine receptor explains the mechanisms for gain- and loss-of function mutations. *Nat Commun*, 13(1):2821, 2022.
2. **M. Kikkawa** and H. Yanagisawa. Identifying proteins in the cell by tagging techniques for cryo-electron microscopy. *Microscopy (Oxf)*, 71(Supplement 1):i60–i65, 2022.
3. H. Nakamura, **M. Kikkawa**, and T. Murata. Technical development and sharing of high-resolution cryo-electron microscopes. *Biophys Physicobiol*, 18:265–266, 2021.
4. T. Sakuragi, R. Kanai, A. Tsutsumi, H. Narita, E. Onishi, K. Nishino, T. Miyazaki, T. Baba, H. Kosako, A. Nakagawa, **M. Kikkawa**, C. Toyoshima, and S. Nagata. The tertiary structure of the human Xkr8-Basigin complex that scrambles phospholipids at plasma membranes. *Nat Struct Mol Biol*, 28(10):825–834, 2021.
5. J. Obata, N. Kawakami, A. Tsutsumi, E. Nasu, K. Miyamoto, **M. Kikkawa**, and R. Arai. Icosahedral 60-meric porous structure of designed supramolecular protein nanoparticle TIP60. *Chem Commun (Camb)*, 57(79):10226–10229, 2021.
6. Y. Zhang, S. Watanabe, A. Tsutsumi, H. Kadokura, **M. Kikkawa**, and K. Inaba. Cryo-EM analysis provides new mechanistic insight into ATP binding to Ca(2+) -ATPase SERCA2b. *EMBO J*, page e108482, 2021.
7. R. Danev, H. Yanagisawa, and **M. Kikkawa**. Cryo-EM Performance Testing of Hardware and Data Acquisition Strategies. *Microscopy (Oxf)*, 2021.

Department of Cytoarchitectonics

Lecturer

Yosuke Tanaka, M. D.

Homepage http://cb.m.u-tokyo.ac.jp/

Teaching activities

Our teaching responsibility is following.

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. Yoshihara S., Jiang X., Morikawa Mo., Ogawa T., Ichinose S., Yabe H., Kakita A., Toyoshima M., Kunii Ya, Yoshikawa T., **Tanaka Y.**, and N. Hirokawa. Betaine ameliorates schizophrenic traits by functionally compensating KIF3-based

CRMP2 transport. ***Cell Rep*** 35: 108971, April 13, 2021.

2. Morikawa Ma, Jerath N. U., Ogawa T., Morikawa Mo, **Tanaka Y.**, Shy M.E., Zuchner, S., and N. Hirokawa. KIF1A mutation of human neuropathies hyperstabilizes the motor-neck interaction in ATPase cycle. ***EMBO J.*** 41(5): e108899, Mar 1, 2022.

Department of Cellular Neurobiology

Professor

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

Research Associate

Yutaro Kashiwagi, Ph.D., Hisato Maruoka, Ph.D., Keiichiro Minatohara, 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 23 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. Kashiwagi, Y., **Okabe, S.** Imaging of spine synapses using super-resolution microscopy. Anatomical Science International 2021 96(3): 343-358 doi: 10.1007/s12565-021-00603-0.
2. Obashi, K, Taraska, J. W., **Okabe, S.** The role of molecular diffusion within dendritic spines in synaptic function. Journal of General Physiology 2021 153(4) e202012814. doi: 10.1085/jgp.202012814.
3. Yoshida T, Yamagata A, Imai A, Kim J, Izumi H, Nakashima S, Shiroshima T, Maeda A, Iwasawa-Okamoto S, Azechi K, Osaka F, Saitoh T, Maenaka K, Shimada T, Fukata Y, Fukata M, Matsumoto J, Nishijo H, Takao K, Tanaka S, **Okabe S,** Tabuchi K, Uemura T, Mishina M, Mori H, Fukai S. Canonical versus non-canonical transsynaptic signaling of neuroligin 3 tunes development of sociality. Nature Communications 2021 12(1):1848. doi: 10.1038/s41467-021-22059-6.
4. Tamada K, Fukumoto K, Toya T, Nakai N, Awasthi JR, Tanaka S, **Okabe S,** Spitz F, Saitow F, Suzuki H, Takumi T. Genetic dissection identifies Necdin as a driver gene in a mouse model of paternal 15q duplications. Nature Communications 2021 12(1):4056. doi: 10.1038/s41467-021-24359-3.
5. Morris K, Nami M, Bolanos JF, Lobo MA, Sadri-Naini M, Fiallos J, Sanchez GE, Bustos T, Chintam N, Amaya M, Strand SE, Mayuku-Dore A, Sakibova I, Biso GMN, DeFilippis A, Bravo D, Tarhan N, Claussen C, Mercado A, Braun S, Yuge L, **Okabe S,** Taghizadeh-Hesary F, Kotliar K, Sadowsky C, Chandra PS, Tripathi M, Katsaros V, Mehling B, Noroozian M, Abbasioun K, Amirjamshidi A, Hossein-Zadeh GA, Naraghi F, Barzegar M, Asadi-Pooya AA, Sahab-Negah S, Sadeghian S, Fahnestock M, Dilbaz N, Hussain N, Mari Z, Thatcher RW, Sipple D, Sidhu K, Chopra D, Costa F, Spena G, Berger T, Zelinsky D, Wheeler CJ, Ashford JW, Schulte R, Nezami MA, Kloor H, Filler A, Eliashiv DS, Sinha D, DeSalles AAF, Sadanand V, Suchkov S, Green K, Metin B, Hariri R, Cormier J, Yamamoto V, Kateb B. Neuroscience20 (BRAIN20, SPINE20, and MENTAL20) Health Initiative: A Global Consortium Addressing the Human and Economic Burden of Brain, Spine, and Mental Disorders Through Neurotech Innovations and Policies J Alzheimers Dis. 2021 83(4):1563-1601. doi: 10.3233/JAD-215190.
6. Quaglio G, Toia P, Moser EI, Karapiperis T, Amunts K, **Okabe S**, Poo MM, Rah JC, Koninck Y, Ngai J, Richards L, Bjaalie JG. The International Brain Initiative: enabling collaborative science. Lancet Neurol. 2021 20(12):985-986. doi: 10.1016/S1474-4422(21)00389-6.
7. Endo M, Maruoka H, **Okabe S.** Advanced Technologies for Local Neural Circuits in the Cerebral Cortex. Front Neuroanat. 2021 15:757499. doi: 10.3389/fnana.2021.757499. eCollection 2021.
8. Terashima H, Minatohara K, Maruoka H, **Okabe S.** Imaging neural circuit pathology of autism spectrum disorders: autism-associated genes, animal models and the application of in vivo two-photon imaging. Microscopy (Oxf). 2022 71(Supplement_1):i81-i99. doi: 10.1093/jmicro/dfab039.
9. Kamei R, Urata S, Maruoka H, **Okabe S.** In vivo Chronic Two-Photon Imaging of Microglia in the Mouse Hippocampus. J Vis Exp. 2022 6;(185). doi: 10.3791/64104.

Molecular Cell Biology

2. Biochemistry and Molecular Biology

Department of Molecular Biology

Professor

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

Lecturer

Hayashi Yamamoto, Ph.D.

Research Associate

Yuji Sakai, Ph.D., Saori Yoshii, M.D., Ph.D.

Project Associate Professor

Chieko Saito, Ph.D.

Project Lecturer

Ikuko Koyama-Honda, Ph.D.

Project Research Associate

Junichi Sakamaki, Ph.D., Tomoya Eguchi, M.D., Ph.D.

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 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 the 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 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 2021, 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.

TMEM41B and VMP1 are endoplasmic reticulum (ER)-localizing multi-spanning membrane proteins required for ER-related cellular processes such as autophagosome formation, lipid droplet homeostasis, and lipoprotein secretion in eukaryotes. Both proteins have a VTT domain, which is similar to the DedA domain found in bacterial DedA family proteins. However, the molecular function and structure of the DedA and VTT domains (collectively referred to as DedA domains) and the evolutionary relationships among the DedA domain-containing proteins are largely unknown. Phylogenetic analysis revealed that the TMEM41, VMP1, DedA, and PF06695 families form a superfamily with a common origin, which we termed the DedA

superfamily. Coevolution-based structural prediction suggests that the DedA domain contains two reentrant loops facing each other in the membrane. This topology is biochemically verified by the substituted cysteine accessibility method. The predicted structure is topologically similar to that of the substrate-binding region of several ion transporters. Thus, we hypothesize that VMP1 and TMEM41B have an ion or lipid transporting activity and that function is important for multiple functions of these proteins in the ER (Okawa et al. *J Cell Sci* 2021).

Autophagy undergoes dynamic positive and negative regulation in response to multiple forms of cellular stress, but the precise mechanisms are not fully understood. To investigate the negative regulatory system of autophagy, we performed a genome-wide CRISPR screen for negative regulators of autophagy, using the GFP-LC3-RFP reporter, which can quantify autophagic activities. We identified phosphoribosylformylglycinamidine synthase (PFAS), a component of the de novo purine synthesis pathway, as a negative regulator of autophagy. Purine starvation-induced autophagy through the TSC-RHEB-mTORC1 signaling axis. Moreover, depletion of pyrimidine synthesis enzymes activated autophagy as well. However, mTORC1 activity was not altered by pyrimidine shortage, suggesting a different mechanism of autophagy induction between purine and pyrimidine starvation. These findings provide novel insights into the regulation of autophagy by metabolites (Mimura et al. *J Biol Chem* 2021).

Phase-separated droplets with liquid-like properties can be degraded by autophagy, but the underlying mechanism is poorly understood. We derived a physical model to investigate the interaction between autophagic membranes and such droplets, uncovering that intrinsic wetting interactions underlie droplet-membrane contacts. We found that the competition between droplet surface tension and the increasing tendency of growing membrane sheets to bend determines whether a droplet is completely engulfed or isolated in a piecemeal fashion, a process we term fluidophagy. Our study provides a physical account of how droplet-membrane wetting underpins the structure and fate of forming autophagosomes (Agudo-Canalejo et al. *Nature* 2021).

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.

In 2021, we revealed a new physiological role for autophagy. It has been known that autophagy regulates primary cilia formation, but the underlying mechanism is not fully understood. We identified NIMA-related kinase 9 (NEK9) as a GABARAPs-interacting protein and found that NEK9 and its LC3-interacting region (LIR) are required for primary cilia formation. Mutation in the LIR of NEK9 in mice also impaired in vivo cilia formation in the kidneys. Mechanistically, NEK9 interacted with MYH9 (also known as myosin IIA), which has been implicated in inhibiting ciliogenesis through stabilization of the actin network. MYH9 accumulated in NEK9 LIR mutant cells and mice, and depletion of MYH9 restores ciliogenesis in NEK9 LIR mutant cells. These results suggest that NEK9 regulates ciliogenesis by acting as an autophagy adaptor for MYH9. Given that the LIR in NEK9 is conserved only in land vertebrates, the acquisition of the autophagic regulation of the NEK9-MYH9 axis in ciliogenesis may have possible adaptive implications for terrestrial life (Yamamoto et al. *Nat Commun* 2021).

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. We have recently developed a new fluorescent reporter, GFP-LC3-RFP-LC3ΔG, to assess autophagic flux. We have

generated a new mouse model ubiquitously expressing this autophagy flux reporter.

4. Autophagy-independent organelle degradation

The eye lens of vertebrates is composed of fiber cells in which all membrane-bound organelles undergo degradation during terminal differentiation to form an organelle-free zone. The mechanism that underlies this large-scale organelle degradation remains largely unknown, although it has previously been shown to be independent of macroautophagy. We found that phospholipases in the PLAAT (phospholipase A/acyltransferase) family are essential for the degradation of lens organelles such as mitochondria, the endoplasmic reticulum, and lysosomes. PLAAT translocates from the cytosol to various organelles immediately before organelle degradation, in a process that requires their C-terminal transmembrane domain. The translocation of PLAAT to organelles depends on the differentiation of fiber cells and damage to organelle membranes, both of which are mediated by Hsf4. After the translocation of PLAAT to membranes, the phospholipase induces extensive organelle rupture that is followed by complete degradation. Organelle degradation by PLAAT-family phospholipases is essential for achieving optimal transparency and refractive function of the lens. These findings expand our understanding of intracellular organelle degradation and provide insights into the mechanism by which vertebrates acquired transparent lenses.

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. Kusumaatmaja, H., May, A.I., Feeney, M., McKenna, J.F., Mizushima, N., Frigerio, L., *Knorr, R.L. Wetting of phase-separated droplets on plant vacuole membranes leads to a competition between tonoplast budding and nanotube formation. ***Proc. Natl. Acad. Sci. USA.*** 118: e2024109118 (2021)
2. Yamamoto, Y., Chino, H., Tsukamoto, S., Ode, KL, Ueda H.R., *Mizushima, N. NEK9 regulates primary cilia formation by acting as a selective autophagy adaptor for MYH9/myosin IIA. ***Nat. Commun.*** 12:3292 (2021)
3. Mimura, K., Sakamaki, J.I., Morishita, H., Kawazu, M., Mano, H., *Mizushima, N. Genome-wide CRISPR screening reveals nucleotide synthesis negatively regulates autophagy ***J. Biol. Chem.*** 296:100780 (2021)
4. *Morishita, H., Eguchi, T., Tsukamoto, S., Sakamaki, Y., Takahashi, S., Saito, C., Koyama-Honda, I., *Mizushima, N. Organelle degradation in the lens by PLAAT phospholipases. ***Nature,*** 592:634-638 (2021)
5. Okawa, F., Hama, Y., Zhang, S., Morishita, H., Yamamoto, H., Levine, T.P., *Mizushima, N. Evolution and insights into the structure and function of the DedA superfamily containing TMEM41B and VMP1. ***J. Cell Sci.*** 134: jcs255877 (2021)
6. Agudo-Canalejo, J., Schultz, S.W., Chino, H., Migliano, S., Saito, C., Koyama-Honda, I., Stenmark, H., Brech, A., May, A.I., Mizushima, N., *Knorr, R. L. Wetting regulates autophagy of phase-separated compartments and the cytosol. ***Nature*** 591:142-146 (2021)
7. Klionsky, D.J. et al. Autophagy in major human diseases. ***EMBO J.*** 40: e108863 (2021)
8. *Morishita, H., Eguchi, T., *Mizushima, N. A new insight into the lens: cytosolic PLAAT phospholipases degrade organelles to make the lens transparent. ***Autophagy*** 17: 2645-2647 (2021)
9. *Mizushima, N., *White E, *Rubinsztein DC. Breakthroughs and bottlenecks in autophagy research. ***Trends Mol. Med.*** 11; S1471-4914(21) 00179-9 (2021)

10. Yamamoto, Y., *Mizushima, N. Autophagy and ciliogenesis. ***JMA J.*** 15:207-215 (2021)
11. Zhang, S., Hama, Y., *Mizushima, N. The evolution of autophagy proteins: diversification in eukaryotes and potential ancestors in prokaryotes. ***J. Cell. Sci.*** 134: jcs233742 (2021).
12. Hama, Y., Zhang, S., *Mizushima, N. ZZ domains keep cytosol to vacuole delivery whiZZing along. ***EMBO J*** 25: e108777 (2021)
13. Klionsky D.J., et al. Guidelines for the use and interpretation of assays for monitoring autophagy (4th edition). ***Autophagy*** 17:1-382 (2021)
14. Morishita, H., Kanda, Y., *Mizushima, N. No air without autophagy: autophagy is important for lung and swim bladder inflation. ***Autophagy,*** 17(4):1040-1041 (2021)
15. Schultz, S.W., Agudo-Canalejo, J., Chino, H., Migliano, S., Saito, C., Koyama-Honda, I., Stenmark, H., Brech, A., Mizushima, N., *Knorr, R. L., *May, A.I. Should I bend or should I grow: the mechanisms of droplet-mediated autophagosome formation. ***Autophagy,*** 17:1046-1048 (2021)
16. Yim, W.W., *Mizushima, N. Autophagosome maturation stymied by SARS-CoV-2. ***Dev. Cell*** 56:400-402 (2021).

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Introduction

The Department of Cellular Signaling, belonging to the Molecular Cell Biology, is organized by Murakami, who is also a professor of the Laboratory of Microenvironmental and Metabolic Health Sciences, from August 2018 to March 2022. The laboratory is composed of one professor and one assistant professor as well as members of the Laboratory of Microenvironmental and Metabolic Health Sciences.

Research activities

The main theme of this research project is to clarify the role of lipids in health and diseases. Lipids represent the largest source of energy in living organisms, are main components constituting cell membranes, and also act as signal molecules. Lipids are environmental nutritional factors ingested from foods, as well as tissue microenvironmental regulators that spatiotemporally coordinate 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 A_2 (PLA_2) 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 previously reported that PLA2G5 ($sPLA_2$-V), secreted from hypertrophic white adipocytes during 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), and that PLA2G2D ($sPLA_2$-IID), secreted from M2-like macrophages in white adipose tissue, releases ω3 polyunsaturated fatty acids (PUFAs) to promote cold-induced adipocyte browning and thereby thermogenesis (Sato et al, *Cell Rep,* 2020). In addition, we have recently found that PLA2G2E ($sPLA_2$-IIE) is highly induced in brown and beige adipocytes in response to cold and that its genetic deletion leads to partial impairment of adipocyte browning and thermogenesis.

Choline supplies methyl groups for regeneration of methionine and the universal methyl donor *S*-adenosylmethionine (SAM) in the liver. Although PC is the main cellular reservoir for choline, the pathway for hepatic PC catabolism that generates free endogenous choline remains unexplored. We found that PNPLA7, a lysophospholipase that catalyzes the hydrolysis of lysophosphatidylcholine (LPC) to glycerophosphocholine (GPC), is crucial for this pathway. *Pnpla7*-deficient mice show marked decreases in hepatic GPC, choline, betaine and SAM, accompanied by various signs of methionine insufficiency including impaired triglyceride storage and secretion, hypoglycemia, increased energy expenditure, reduced fat mass with adipocyte

browning, and decreased epigenetic histone and DNA methylation. Accordingly, *Pnpla7*$^{-/-}$ mice are lean, display growth retardation, and die prematurely. We further found that mice lacking PNPLA8 (iPLA$_2$γ), which acts as PLA$_1$/A$_2$, recapitulate most of these phenotypes, suggesting that PNPLA8 lies upstream of PNPLA7. Thus, the methyl group flux from choline endogenously generated through PC breakdown by the PNPLA8-PNPLA7 axis is essential for liver functions and systemic energy homeostasis (submitted).

2) Skin diseases

Lipids play crucial roles in skin homeostasis and diseases. We previously reported that PLA2G2F (sPLA$_2$-IIF), which is specifically expressed in epidermal keratinocytes, mobilizes lysoplasmalogen, a unique lysophospholipid that promotes epidermal hyperplasic diseases such as psoriasis and skin cancer (Yamamoto et al, *J Exp Med,* 2015), and that PNPLA1, a member of the intracellular iPLA$_2$ family whose mutations cause autosomal recessive congenital ichthyosis, acts as a transacylase to produce ω-*O*-acylceramide, an essential lipid for skin barrier function (Hirabayashi et al, *Nat Commun,* 2017). PLA2G4E (cPLA$_2$ε), which is expressed in epidermal keratinocytes, exhibits a unique *N*-acyltransferase activity that transfers a fatty acid from the *sn*-1 position of PC to the amino group of phosphatidylethanolamine (PE) to give rise to *N*-acyl PE (NAPE), a precursor of the non-canonical bioactive lipid *N*-acylethanolamine (NAE). *Pla2g4e*-deficient mice display exacerbation of psoriasis with marked reduction of various NAE species, suggesting that PLA2G4E plays a role in putting a brake on psoriasis by generating the anti-inflammatory lipid mediator NAE (Liang et al, *FASEB J* 2022).

PLA2G3 (sPLA$_2$-III) is expressed in epidermal keratinocytes and its global or skin-specific deletion leads to perturbation of skin barrier function due to fragile cornified envelope and loosened epidermal tight junction. Accordingly, following topical antigen challenge, global or skin-specific *Pla2g3*-deficient mice display more severe atopic dermatitis-like symptoms with increased expression of type 2 cytokines, serum IgE levels, eosinophil infiltration, scratching behavior, and disturbed skin microbiota. Global or skin-specific deletion of EP4 (PGE$_2$ receptor) or FP (PGF$_{2\alpha}$ receptor) largely if not solely recapitulate these phenotypes, and treatment with FP or EP4 agonists rescue skin abnormalities in *Pla2g3*-deficient mice. Moreover, global or skin-specific *Pla2g3*-deficient mice exhibited more severe asthma following topical antigen challenge. These results suggest that the PLA2G3-driven PGE$_2$-EP4/PGF$_{2\alpha}$-FP signaling in keratinocytes plays an important role in skin barrier formation and thereby skin homeostasis, perturbation of which leads to exacerbation of atopic march.

3) Allergic and other immunological diseases

We previously reported that PLA2G3, an sPLA$_2$ isoform secreted from mast cells (MCs), promotes MC maturation by driving the paracrine PGD$_2$ circuit in cooperation with microenvironmental fibroblasts (Taketomi et al, *Nat Immunol* 2013; Taketomi et al, *Cells* 2021) and that PAF-AH2, a unique PLA$_2$ that hydrolyzes oxidized phospholipids, ensures optimal MC activation and thereby allergic responses through producing unique EPA/DHA metabolites (ω3 epoxides) (Shimanaka et al, *Nat Med* 2017). Furthermore, we have recently found that PLA2G3 is also coupled with an additional lipid mediator, lysophosphatidic acid (LPA), which acts in concert with PGD$_2$ to facilitate MC maturation.

PLA$_2$ subtypes that regulate T cell immunity are unknown. By transcriptional and functional screening of PLA$_2$ enzymes expressed in T cells, we have found that PLA2G12A (sPLA$_2$-XIIA) is induced in Th17 cells and participates in Th17 differentiation. Global or CD4$^+$ T cell-specific *Pla2g12a*-deficient mice have lower psoriatic inflammation with decreased Th17 and γδT cells in the skin and lymph nodes. We are now analyzing a particular lipid mediator that acts downstream of PLA2G12A in inducing Th17 immunity.

4) Gut microbiota

Despite the restricted intestinal expression of PLA2G2A (sPLA$_2$-IIA) in BALB/c mice, its genetic deletion leads to amelioration of skin carcinogenesis. Metagenome, transcriptome and metabolome analyses have revealed that *Pla2g2a* deficiency alters the gut microbiota, accompanied by notable changes in the intestinal expression of genes related to immunity and metabolism as well as the levels of various blood metabolites and fecal bacterial lipids, suggesting that

PLA2G2A contributes to shaping of the gut microbiota (Miki et al, *JCI Insight*, 2022). *Pla2g2a*$^{-/-}$ mice also display an alteration in passive cutaneous anaphylaxis (Taketomi et al, *Metabolites* 2022). These results highlight a new aspect of PLA2G2A as a modulator of gut microbiota, perturbation of which affects distal skin responses.

5) Cancer

Extracellular vesicles (EVs) including exosomes act as intercellular communicators by transferring protein and microRNA cargoes, yet the role of EV lipids remains unclear. We have recently found that the pro-tumorigenic action of lymphoma-derived EVs is augmented via $sPLA_2$-driven lipid metabolism. Hydrolysis of EV phospholipids by PLA2G10 ($sPLA_2$-X), which is induced in a specific population of macrophages in Epstein-Barr virus (EBV)-induced lymphoma, increases the production of fatty acids, lysophospholipids and their metabolites. Additionally, $sPLA_2$-treated EVs are smaller, self-aggregate, show better uptake, and increase cytokine expression and lipid mediator signaling in recipient tumor-associated macrophages. Lymphoma growth in EBV-infected mice is suppressed by a $sPLA_2$ inhibitor, while treating the mice with $sPLA_2$-modified EVs can reverse this phenotype. Thus, the $sPLA_2$-driven EV modification promotes tumor development (Kudo et al, *Cell Metab* 2022). It is anticipated that modification of EVs by $sPLA_2$s may occur universally in various cancers as well as in allergic and metabolic diseases, a possibility that is currently under investigation.

6) Infectious diseases

PLA2G2D expressed in dendritic cells and M2 macrophages attenuates anti-viral Th1 immunity by supplying ω3 PUFAs and PGD_2 (Miki et al, *J Exp Med* 2013). In collaboration with a foreign group, we have reported that *Pla2g2d* deficiency protects mice from pneumonia caused by coronavirus infection (Roy Wong et al, *Nature* 2022). Therefore, PLA2G2D may be an attractive drug target for treatment of COVID-19.

7) Neuronal and retinal diseases

Mutations in the *PNPLA6* gene cause neuronal and retinal degeneration such as hereditary spastic paraplegia (SPG39), Boucher-Neuhauser syndrome, Oliver-McFariane syndrome, and Laurence-Moon syndrome. PNPLA6 acts a phospholipase B (PLA_1/A_2 + lysophospholipase), hydrolyzing PC to give rise to two fatty acids and GPC, in cells. Intriguingly, neuron-specific deletion of PNPLA6 and its closest homolog PNPLA7 leads to neurodegenerative disorders similar to hereditary spastic paraplegia and that tamoxifen-inducible eye-specific deletion of PNPLA6 results in retinal degeneration. Retinal degeneration in these mice can be prevented by eye drops of choline, a PC degradation product. Clarifying the regulatory roles of lipid metabolism driven by PNPLA6/PNPLA7 will shed light on the molecular mechanism underlying the PNPLA6-related neuronal and retinal disorders.

Furthermore, in collaboration with an external group, we found that a particular $sPLA_2$ isoform that is induced after cerebral infarction is involved in neuroprotection by mobilizing a unique lipid mediator (submitted).

Teaching activities

The Department of Cellular Signaling has important missions to train postdoctoral fellows to become promising scientist leaders in the field of medical sciences and to provide biochemistry and molecular biology 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 have been provided to medical students (M0). Four undergraduate students (three M2 students and one M4 student) participate in the Murakami's team throughout the year.

Publications

1. Miki Y, Taketomi Y, Kidoguchi Y, Yamamoto K, Muramatsu K, Nishito Y, Park J, Hosomi K, Mizuguchi K, Kunisawa J, Soga T, Boilard E, Gowda SGB, Ikeda K, Arita M, Murakami M. Group IIA secreted phospholipase A_2 controls

skin carcinogenesis and psoriasis by shaping the gut microbiota. *JCI Insight.* 7, e152611, 2022.

2. Doré E, Joly-Beauparlant C, Morozumi S, Mathieu A, Lévesque T, Allaeys I, Duchez AC, Cloutier N, Leclercq M, Bodein A, Payré C, Martin C, Petit-Paitel A, Gelb MH, Rangachari M, Murakami M, Davidovic L, Flamand N, Arita M, Lambeau G, Droit A, Boilard E. The interaction of secreted phospholipase A_2-IIA with the microbiota alters its lipidome and promotes inflammation. *JCI Insight*. 7, e152638, 2022.
3. Kudo K, Miki Y, Carreras J, Nakayama S, Nakamoto Y, Ito M, Nagashima E, Yamamoto K, Higuchi H, Morita S, Inoue A, Aoki J, Ando K, Nakamura N, Murakami M, Kotani A. Secreted phospholipase A_2 modifies extracellular vesicles and accelerates B-cell lymphoma. *Cell Metab.* 34, 1-19, 2022.
4. Roy Wong LY, Zheng J, Wilhelmsen K, Li K, Ortiz ME, Schnicker NJ, Pezzulo AA, Szachowicz PJ, Klumpp K, Aswad F, Rebo J, Narumiya S, Murakami M, Meyerholz DK, Fortney K, McCray PB, Perlman S. Eicosanoid signaling as a therapeutic target in middle-aged mice with severe COVID-19. *Nature*. 605, 146-151, 2022.
5. Shibata T, Kawana H, Nishino Y, Ito Y, Sato H, Onishi H, Kano K, Inoue A, Taketomi Y, Murakami M, Kofuji S, Nishina H, Miyazawa A, Kono N, Aoki J. Abnormal male reproduction and embryonic development induced by downregulation of a phospholipid fatty acid-introducing enzyme Lpgat1 in zebrafish. *Sci Rep*. 12, 7312, 2022.
6. Liang L, Takamiya R, Miki Y, Heike K, Taketomi Y, Sugimoto N, Yamaguchi M, Shitara H. Nishito Y, Kobayashi T, Hirabayashi T, Murakami M. Group IVE cytosolic phospholipase A_2 limits psoriatic inflammation by mobilizing the anti-inflammatory lipid *N*-acylethanolamine. *FASEB J.* 36, e22301, 2022.
7. Taketomi Y, Miki Y, Murakami M. Old but new: Group IIA phospholipase A_2 as a modulator of gut microbiota. *Metabolites*. 12, 352, 2022. (Review)

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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, 2 postdoctoral fellows, 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. In another work, we clarified that the tympanic membranes of mammals and reptiles/birds are independently acquired as a product of convergent evolution by showing that lower-to-upper jaw

transformation induced by inactivation of ET-1/ETAR signaling results in loss of the tympanic membrane in mouse, but causes duplication of the tympanic membrane in chicken. Recently, human ETAR gene mutations causing craniofacial abnormalities and alopecia were identified, and the causal relationship was confirmed by our experiments recapitulating the same mutations in mice. We are now collaborating researchers in the field of molecular dynamics to clarify the mechanisms underlying the pathogenic mutations.

Furthermore, we demonstrated that the therian mammal's premaxilla (rostralmost upper jaw bone) is derived from the maxillary prominence of the mandibular arch through comparative morphological and developmental analyses. The developmental primordium that produces the premaxilla in non-mammalian tetrapods rarely contributes to the upper jaw in therian mammals, but rather forms a motile nose. We propose that these previously unrecognized rearrangements allowed key innovations, such as the highly sensible tactile perception and olfactory function, in mammalian evolution.

(2) Cardiac development

Recently, we found that the cranial neural crest from the preotic region, rather than post-otic 'cardiac' neural crest cells, migrate into the heart and differentiate into coronary artery smooth muscle cells in the proximal region. Ablation of the preotic neural crest in chick embryos causes abnormalities in coronary septal branch and orifice formation. Appropriate migration and deployment of neural crest cells and subsequent smooth muscle differentiation require multicellular interactions involving ET-1/ETAR signaling possibly through $G_{12/13}$-mediated, Dlx5/Dlx6-independet mechanisms, whereas ET-1/ETAR signaling is involved in ventral identification of the pharyngeal arches through $G_{q/11}$-mediated, Dlx5/Dlx6-dependet mechanisms. These findings indicate that the ET-1/ETAR signaling pathway is involved in craniofacial and cardiac development through different trimeric G-proteins.

(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) and his colleagues, to elucidate the possible cellular mechanisms underlying branch formation in angiogenesis.

References

1. Vu TH, Takechi M, Shimizu M, Kitazawa T, Higashiyama H, Iwase A, Kurihara H, Iseki S. Dlx5-augmentation in neural crest cells reveals early development and differentiation potential of mouse apical head mesenchyme. Sci. Rep. 11(1):2092, 2021.
2. Arima Y, Nakagawa Y, Takeo T, Ishida T, Yamada T, Hino S, Nakao M, Hanada S, Umemoto T, Suda T, Sakuma T, Yamamoto T, Watanabe T, Nagaoka K, Tanaka Y, Kawamura YK, Tonami K, Kurihara H, Sato Y, Yamagata K, Nakamura T, Araki S, Yamamoto E, Izumiya Y, Sakamoto K, Kaikita K, Matsushita K, Nishiyama K, Nakagata N, Tsujita K. Murine neonatal ketogenesis preserves mitochondrial energetics by preventing protein hyper-acetylation. Nat Metab. 3(2):196-210, 2021.
3. Maruyama K, Naemura K, Arima Y, Uchijima Y, Nagao H, Yoshihara K, Singh MK, Uemura A, Matsuzaki F, Yoshida Y, Kurihara Y, Wada Y,

Miyagawa-Tomita S, Kurihara H. Semaphorin3E-PlexinD1 signaling is required for coronary artery and lymphatic vessel development, with clinical implications in myocardial recovery. iScience 24(4):102305, 2021.

4. Maruyama K, Naemura K, Yoshihara K, Imanaka-Yoshida K, Kurihara H, Miyagawa-Tomita S. Surgical protocol for permanent ligation of the left anterior descending coronary artery in mice to generate a model of myocardial infarction. STAR Protoc. 2(3):100775, 2021.
5. Higashiyama H, Koyabu D, Hirasawa T, Werneburg I, Kuratani S, Kurihara H. Mammalian face as an evolutionary novelty. Proc. Natl. Acad Sci. U.S.A. 118(44): e2111876118, 2021.
6. Kurihara H, Mada J, Tokihiro T, Tonami K, Ushijima T, Yura F. Angiogenesis: dynamics of endothelial cells in sprouting and bifurcation. In Mathematical Modeling for Genes to Collective Cell Dynamics (ed. Tokihiro T. Springer, Singapore) pp. 25-83, 2021.
7. 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.
8. Higashiyama H, Koyabu D, Kurihara H. Evolution of the therian face through complete loss of the premaxilla. Evol. Dev. (in press)
9. 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. (in press)

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Introduction and Organization

Our laboratory was established in 2018. We are supported by grants from the Japan Science and Technology Agency (JST), the Japan Society for the Promotion of Science (JSPS) and Takeda Science Foundation. Our research also benefits from indirect support through an instrumentation facility grant from the Japan Agency for Medical Research and Development (AMED). The lab members are Radostin Danev (professor) and Fabian Eisenstein (JSPS fellow).

Teaching activities

We conduct training and provide support for the users of the recently opened cryo-electron microscopy (cryo-EM) facility at the Graduate School of Medicine. This includes specialized lectures at cryo-EM courses within the University of Tokyo and other research institutions in Japan and abroad. We also give introductory lectures about 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
5) Biophysical Chemistry II course at the School of Science

Research activities

Our research is aimed at elucidating the structure-function relationships of proteins and cellular components. Through our work, we hope to contribute to the fundamental knowledge about the molecular mechanisms behind chronic diseases, and thereby to help develop effective treatments.

For the past four years, we have been investigating an important class of membrane proteins called G protein-coupled receptors (GPCRs). GPCRs constitute the largest family of membrane proteins in the human genome. They are responsible for the detection and transduction of many extracellular signals that regulate various physiological processes across the plasma membrane. Because of their broad regulatory functions, GPCRs are implicated in numerous chronic diseases, such as diabetes, obesity, nervous system disorders, migraine, asthma, allergies, cardiovascular disorders, cancer, and others. Consequently, they also represent the biggest group of drug targets and are the subject of more than 30% of approved drugs.

To understand the mechanisms of GPCR activation and signal transduction at the atomic level, we use the modern and very prolific method of cryo-EM single particle analysis. In an ongoing international collaboration with a group at Monash University in Australia, which specializes in GPCR pharmacology and has substantial experience in expression and purification of target complexes, we are studying receptor activation by both native and synthetic

ligands. In the past three years, our results comprise more than 40 sub-3 Å unmodified full-length GPCR structures, approximately half of which are at resolutions better than 2.5 Å. This is an unprecedented achievement in structural biology, both in terms of the number of structures and their resolution. Our success is not coincidental. To reach such a level of performance, we conducted a careful systematic quantification and optimization of the cryo-EM experimental parameters for sample preparation and data collection. We adopted a highly efficient synergistic experimental approach that combined data collection from real samples with testing of individual experimental factors. The method had the advantage of not requiring extra observation time on the costly and heavily booked electron cryo-microscopes. The results from this work led us toward a better experimental design and allowed us to routinely produce sub-2.5 Å resolution results in our recent studies. Most prominently, in the summer of 2020 we were able to produce the first sub-2 Å resolution reconstructions of GPCR complexes.

2020 was also the year when true cryo-EM atomic resolution (~1.2 Å) was demonstrated by two groups in the UK and Germany with “easy” test samples. In their experiments, they used newly developed hardware components to achieve such performance. We were also able to reach very similar (~1.3 Å) resolution while testing the newly installed Krios G4 microscope at our facility, which has an “off-the-shelf” configuration and does not contain special hardware. The exceptional results from our group and many other groups that utilize the state-of-the-art cryo-EM facility at the University of Tokyo showcase both the accelerating evolution of cryo-EM as a technique and the great success and productivity of the facility.

Despite the rapid growth of the cryo-EM field, there are still many areas where further advances are possible and/or needed. To address such quiescent areas, in addition to our GPCR structural studies we are working on the development of new experimental methods for cryo-EM. One of our current projects aims to develop and implement a high-speed real-time synchronous modulation of the electron beam that will expand the capabilities of the microscope. With the so-called FADE method (fast and accurate defocus modulation), we hope to transform the instrument from a static and rigid system into a dynamic and tunable optical platform. This will give researchers more freedom to tune their experiments for optimal performance. We finished the development and construction of the first FADE hardware prototype, and it is already installed on one of the microscopes at the facility (JEOL JEM-F200). After initial testing with non-biological test samples and resolving several practical issues, the FADE system is now fully operational, and we have started collecting FADE datasets of biological cryo-samples. Hardware-wise, the system performs as expected and produces data of high quality. The main challenge at present is the analysis of the data. All existing software packages for cryo-EM data processing are designed for conventional constant defocus data. To process FADE data, we must modify or write our own data processing routines and we are currently working in this direction.

Other areas of our research include cryo-electron tomography (cryo-ET) of cellular samples, in combination with advanced sample preparation through cryogenic focused ion beam milling (cryo-FIB). The ability to observe proteins and complexes in their native environment within a cell, “in situ”, offers tremendous opportunities for fundamental biological, pharmacological, and medical contributions. Nevertheless, the cryo-ET field is still in its infancy and there are multiple challenges related to sample preparation and data acquisition. This makes the research even more interesting and rewarding. In the coming years, we hope to make contributions to the methodology and achievements of cryo-ET and help to one day reach the ultimate (utopian) goal of “visual proteomics”; where researchers will be able to identify each individual protein and its interactions with neighboring proteins within an electron cryo-tomogram of a cellular volume.

In the near future, we plan to expand our investigations towards state-of-the-art deep learning experiment automation for both cryo-EM single particle analysis and cryo-electron tomography. Deep learning (DL) methods have become ubiquitous, and it is surprising that at present there are no DL-based automation frameworks for cryo-EM and cryo-ET.

Currently, many steps during an experiment are performed manually. Most of these actions involve image evaluation and feature recognition and are therefore perfect candidates for DL algorithms, which have already proven to be capable of human-level performance in such tasks. With more automation, the experiments will become more efficient, for example, allowing researchers to easily operate the microscopes remotely while working on other important tasks. The quality and amount of data will improve and thereby the level and number of scientific results will increase.

References

1. Josephs TM, Belousoff MJ, Liang YL, Piper SJ, Cao J, Garama DJ, Leach K, Gregory KJ, Christopoulos A, Hay DL, Danev R, Wootten D, Sexton PM. Structure and dynamics of the CGRP receptor in apo and peptide-bound forms. Science. 2021 Apr 9;372(6538):eabf7258.
2. Danev R. Practical considerations: defocus, stigmation, coma-free illumination, and phase plates. In: Glaeser RM, Nogales E, Chiu W, editors. Single-particle Cryo-EM of Biological Macromolecules. IOP Publishing. 2021
3. Mobbs JI, Belousoff MJ, Harikumar KG, Piper SJ, Xu X, Furness SGB, Venugopal H, Christopoulos A, Danev R, Wootten D, Thal DM, Miller LJ, Sexton PM. Structures of the human cholecystokinin 1 (CCK1) receptor bound to Gs and Gq mimetic proteins provide insight into mechanisms of G protein selectivity. PLoS Biol. 2021 Jun 4;19(6):e3001295.
4. Zhang X, Belousoff MJ, Liang YL, Danev R, Sexton PM, Wootten D. Structure and dynamics of semaglutide- and taspoglutide-bound GLP-1R-Gs complexes. Cell Rep. 2021 Jul 13;36(2): 109374.
5. Danev R, Belousoff M, Liang YL, Zhang X, Eisenstein F, Wootten D, Sexton PM. Routine sub-2.5 Å cryo-EM structure determination of GPCRs. Nat Commun. 2021 Jul 15;12(1):4333.
6. Draper-Joyce CJ, Bhola R, Wang J, Bhattarai A, Nguyen ATN, Cowie-Kent I, O'Sullivan K, Chia LY, Venugopal H, Valant C, Thal DM, Wootten D, Panel N, Carlsson J, Christie MJ, White PJ, Scammells P, May LT, Sexton PM, Danev R, Miao Y, Glukhova A, Imlach WL, Christopoulos A. Positive allosteric mechanisms of adenosine A1 receptor-mediated analgesia. Nature. 2021 Sep;597(7877):571-576.
7. Zhang X, Johnson RM, Drulyte I, Yu L, Kotecha A, Danev R, Wootten D, Sexton PM, Belousoff MJ. Evolving cryo-EM structural approaches for GPCR drug discovery. Structure. 2021 Sep 2; 29(9):963-974.e6.
8. Johnson RM, Zhang X, Piper SJ, Nettleton TJ, Vandekolk TH, Langmead CJ, Danev R, Sexton PM, Wootten D. Cryo-EM structure of the dual incretin receptor agonist, peptide-19, in complex with the glucagon-like peptide-1 receptor. Biochem Biophys Res Commun. 2021 Nov 12; 578:84-90.
9. Danev R, Yanagisawa H, Kikkawa M. Cryo-EM performance testing of hardware and data acquisition strategies. Microscopy (Oxf). 2021 Nov 24;70(6):487-497.

Functional Biology

1. Physiology

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Introduction

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.

Teaching activities

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 activities

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

(1) Integration of information processed separately in distributed brain regions is essential for brain function. This integration is supported by long-range projection neurons that connect distant brain regions. Information that long-range projection neurons send to their projection targets depends on the cooperative interactions among these neurons. However, how this interaction is realized in cortical circuits is not well understood. We investigated this interaction using

callosal projection neurons (CPNs) in layer 2/3 of mouse visual cortex as a model of long-range projections.

Retrograde dye was injected into the visual cortex of one hemisphere, and CPNs in the opposite hemisphere were retrogradely labeled. Subsequently, using two-photon calcium imaging, visual response properties were compared between CPNs and other cells (non-CPNs). In the non-CPNs, many cells responded to visual stimuli presented on the contralateral eye or on both eyes, and fewer cells responded selectively to the stimuli to the ipsilateral eye. In contrast, some CPN responded selectively to visual inputs from the ipsilateral eye. In addition, CPN cell pairs showed more synchronized activity compared to other pairs, CPNs -non-CPNs or pairs of non-CPNs. To examine synaptic connections between CPNs, we conducted patch-clamp recording from cell pairs in the brain slice preparation. We found more direct synaptic connections in the pairs of CPNs than other cell pairs.

These results indicate that CPNs form a functional network through direct synaptic connections between CPNs. The results also suggest functional networks dependent on the projection target as a universal property of the cortical network.

(2) The cerebral cortex is characterized by a cluster of neurons with similar response properties. Although there exist functional maps (functional architectures) such as orientation selectivity columns in the primary visual cortex (V1), the functional architecture of color information has not been well understood in primates.

In V1, the CO blob (blob) is known as a histologically identified structure. Since many cells within the blob show color selective responses, it is thought that the blob corresponds to a functional architecture dedicated to color representation. Intrinsic imaging that has a low spatial resolution support this view, whereas some electrophysiological studies could not identify clear cluster of color selectivity neurons corresponding to the blob. Thus, the functional architecture of color representation has not been confirmed. We therefore performed two-photon calcium imaging to investigate fine arrangements of the functional architecture of color representation in monkey V1.

We examined color responses using spatially uniform color stimuli and found that neurons responding to the color stimuli formed clusters that coincided with blobs. Furthermore, these clusters had columnar substructures, each composed of a population of cells with specific color selectivity.

Cells within the blob are known to respond well to low spatial frequency stimuli. Color selectivity neurons also respond to lines or bars with specific orientations. Therefore, the above results could be attributed to the use of spatially uniform stimuli. Therefore, we used oriented, drifting color stimuli. These stimuli revealed the clusters built on the same substructural framework but with larger subdomains beyond blobs.

These results suggest that V1 has a functional architecture for color representation that switches between blobs and blob/interblob system based on spatial structure of the visual scene.

References

(1) Kenta Hagihara, Ayako Wendy Ishikawa, Yumiko Yoshimura, Yoshiaki Tagawa, Kenichi Ohki. Long-Range Interhemispheric Projection Neurons Show Biased Response Properties and Fine-Scale Local Subnetworks in Mouse Visual Cortex ***Cerebral Cortex***, 2021, 31 (2), 1307–1315.

(2) Soumya Chatterjee, Kenichi Ohki, R Clay Reid Chromatic micromaps in primary visual cortex ***Nature Communications***, 2021, 12(1):2315, 1-9.

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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, 1 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) Neuronal representations of reward-predicting cues and outcome history with movement in the frontal cortex

The transformation of sensory signals to action is crucial for survival in all animals. An outcome following a sensory signal updates the value of the sensory signal. This updated value is then used in the next response to the same sensory signal to evoke a specific action to obtain or avoid an outcome. In decision-making tasks that require goal-directed actions to successfully receive a reward, task-related and movement-related activities are widely distributed over the whole dorsal neocortex and whole brain.

To clarify action-type-independent decision-making-related information in M2, which plays critical roles in value estimation, action selection, working memory, and motor planning in the rodent, it is necessary to measure the activities of individual neurons within subdivisions of M2 during simple tasks and to analyze how individual neurons encode the multiple types of information. We assumed that the neuronal representations of the cue value and outcome information in classical conditioning, a condition that does not require the learning of an association between a specific action and its consequence, is the basis for the processes of the transformation of sensory cues to appropriate motor actions.

To extract these information types, we trained head-fixed mice to perform a classical conditioning task with two sound cues assigned to different probabilities of water delivery. In addition, in the late stage of learning, we conducted two-photon calcium imaging of three dorsal frontal areas up to a depth of 800 μm from the cortical surface (dorsomedial frontal cortex [dmFrC], dorsolateral frontal cortex [dlFrC], and M1 corresponding to the caudal forelimb motor area, and the medial prefrontal cortex at depths of 800–1200 μm (mPFC). Although licking movement dominated the area-averaged activity over the whole dorsal neocortex, dmFrC affected other dorsal frontal cortical activities, and its inhibition extinguished differences in anticipatory licking between the cues. Many dorsal frontal and medial prefrontal cortical neurons were task-related. Approximately 40% of them were more excited by the low-reward-predicting cue or unrewarded outcomes than by the high-reward-predicting cue or rewarded outcomes, respectively. Task-related activities of these neurons and the others were counterbalanced, so that population activity appeared dominated by licking. The reward-predicting cue and outcome history were most strongly represented in dmFrC.

The Granger causality analysis of the cortex-wide neuronal activity suggests a flow of licking-unaffected information from dmFrC to dlFrC and M1 during the cue period. The photoinhibition experiment showed that the inhibition of dmFrC increased the anticipatory licking in cue B trials more than it did in cue A trials. The regression model and clustering analysis of individual neuronal activity suggest that the proportion of neurons that were more active during presentation of cue B than during presentation of cue A was highest in dmFrC. From these results, we propose that dmFrC played a critical role in suppression of the anticipatory licking in cue B trials, and generally, that dmFrC neurons can initiate other dorsal frontal cortical activity in the decision-making process, on the basis of the cue value. Our results also suggest that the balance of distinct subsets of neurons that are active in response to a cue value (or outcome) and a second cue (or outcome), which were observed even in the condition without appropriate action selection, are the foundation for decision-making processes over time.

(2) Calcium imaging of the neural activity underlying mismatch negativity in common marmosets

Auditory mismatch negativity (MMN) is an event-related potential that reflects the preattentive detection of changes in repetitive and predictive tone sequence. The amplitude of the MMN is attenuated in psychotic disorders, including schizophrenia, and thus is a promising biomarker of these disorders (Näätänen, 2003). Indeed, human electroencephalography studies suggest that the duration of mismatch negativity (dMMN), which is generated by changes in the duration of the presentation stimulus of an oddball task, can be used for early diagnosis of schizophrenia (Koshiyama, et al., 2017). However, electro-encephalography is not sufficient to reveal how the dMMN is represented at the neural circuit level in auditory cortical areas because of the limited spatial resolution. To investigate the special processing mechanisms of dMMN responses in auditory cortical areas, we applied one-photon and two-photon calcium imaging to record neuronal activity in common

marmosets. Marmosets are known as a highly vocal primate species and have three hierarchically connected auditory areas (core, belt, and parabelt), similar to that in humans. Moreover, these areas are suitable for calcium imaging because the surface of the marmoset auditory cortex is outside the lateral sulcus.

We have shown the functional maps and dMMN responses of the core auditory areas. First, we obtained the best frequency maps in awake marmosets. The tonotopic organization of the maps was consistent with previous studies utilizing other recording methods (extracellular recording [Bendor & Wang, 2008], voltage-sensitive dye imaging [Nishimura, et al., 2017], and intrinsic signal imaging [Tani, et al., 2018]). The cellular frequency selectivity within the same local region at different focal depths was also similar to that described previously (Zeng, et al., 2019). Second, the deviance detection responses in the dMMN tasks were clearly detected by one-photon calcium imaging, and the responses at each imaging region were induced by its best frequency. The responses were also recorded from layers I and II/III of the core region by two-photon imaging. Third, we found that subanesthetic doses of ketamine inhibited the calcium responses for deviance detection. This study provides new insights into the spatial representation of neural activities for deviance detection in primate brain.
(From abstract in the 44th Annual Meeting of the Japan Neuroscience Meeting)

(3) Super-wide-field high-speed two-photon imaging and photo-manipulation microscopy of brain activity

Brain activity consists of the coordinated activity of a very large number of neurons. Each region of the brain processes different information and transfers the computed information to another region. Therefore, to understand information processing in a local region, it is necessary to measure many neuronal activities in that region simultaneously, and to understand information processing for the output of individual functions such as behavior, it is necessary to measure neuronal activities in multiple regions simultaneously. We reported an super-wide-field two-photon microscope in 2018 that makes this possible, and in this study we have accelerated this imaging and established a 10 Hz imaging method with two fields of view that are separated. The rotation method of the small device, which is placed between the objective lens and the cortical surface to move the field of view, was changed from the three-stage gear system presented in 2018 to a belt system. This was achieved by improving elemental components to optimize operation, such as minimizing vibration during rotation. A recently developed photodetector that is durable to visible light incidence stronger than fluorescence intensity and an LED light source were newly introduced to the microscope system. After evaluating the detector's over-response to photostimulation, we developed a method to detect neuronal response activity at a video rate without detector over-response by strictly controlling the timing of photostimulation. By optimizing the expression of molecular probes for optogenetics and calcium probes, as well as the stimulation light intensity and conditions for simultaneous imaging, we were able to increase the efficiency of photostimulation and obtain responses with a high signal-to-noise ratio.
We demonstrated that these methods can be applied to the measurement and manipulation of neuronal activity in mouse M2 and M1. We trained head-fixed mice to perform a task in which pulling a lever with the right forelimb was rewarded with a water reward. We expressed light-responsive proteins in the motor cortex neurons of these mice using adeno-associated viruses (AAVs). Simultaneous measurement of M2 and M1 activity during task execution (10 Hz continuous measurement) and statistical analysis of the activity allowed us to quantitatively demonstrate the hierarchy of activity (time course of activity, pattern of pre-motor activity, amount of cellular activity information, etc.). Both regions represented well the forelimb motor information, but the modalities differed not only in single cells but also in populations. We also demonstrated that transient manipulation of the neuronal activity input to M2 can also induce changes in M2 neuronal activity and behavior according to the timing of the manipulation.

(4) Development of an automated injection robot that enables wide-field calcium imaging of more

than 10,000 neurons

Robotics has played a major role in the advancement of biological research over the past few decades. In the neurosciences, experimental manipulations, such as craniotomy, whole-cell patch clamping, and electrode implantation, have been automated, ensuring not only stable and accurate operations, but also facilitating the spread of advanced neurotechnology. The injection of AAVs is one of the most commonly used experimental manipulations in the neurosciences. However, despite it being a time-consuming technique requiring considerable skill on the part of the operator, there have been no reports of its automation so far.

We constructed an automated virus injection robot that enables precise and repetitive injection. There were two major challenges that had to be overcome to develop this injection robot, namely individual differences in brain surface and preservation of the vascular network. We overcame the former by measuring the brain surface with an infrared-distance sensor precisely controlled by a multi-axis robot, and the latter by adopting an image recognition technology that recognizes blood vessels and an algorithm that distributes injection sites in a spatially even pattern without damaging vessels.

To demonstrate the utility of this new methodology, we conducted wide-field Ca^{2+} imaging of mice multi-site injected with a Ca^{2+} indicator. By injecting a small amount of undiluted AAV solution into more than 100 sites in a 6 × 8 mm^2 area of the dorsal cerebral cortex, we were able to deliver AAV widely and uniformly. Furthermore, owing to the precise and fast manipulation of the robot, each injection cycle took only about 20 seconds to complete, and all the injection cycles took about one hour. We also succeeded in recording cellular-level signals from more than 10,000 neurons simultaneously in a single focal plane using an epifluorescence microscope.

The application of this system is not limited to wide-field Ca^{2+} imaging in mice. This approach would be applicable not only to other animals, such as marmosets or macaques, but also to the monitoring of a wide range of sensor proteins."

(From abstract in the 44th Annual Meeting of the Japan Neuroscience Meeting)

References

1. Matsuzaki M. and Ebina T. Optical deep-cortex exploration in behaving rhesus macaques. Nature Communications 12, 4656, 2021. (Comment)
2. Inoue T., Terada S., Matsuzaki M., and Izawa J.A small-scale robotic manipulandum for motor control study with rodents. Advanced Robotics 35, 898-906, 2021.
3. Kondo M. and Matsuzaki M. Neuronal representations of reward-predicting cues and outcome history with movement in the frontal cortex. Cell Reports 34, 108704, 2021.
4. Okamoto K., Ebina T., Fuji N., Konishi K., Sato Y., Kashima T., Nakano R., Hioki H., Takeuchi H., Yumoto J., Matsuzaki M., and Ikegaya Y. Tb^{3+}-doped fluorescent glass pipettes for biology. Science Advances 7, eabd2529, 2021.

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Introduction and Organization

This laboratory was founded in 1953 as Department of Neurophysiology, Institute for Brain Research. In 1997, 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 fellows, 8 graduate students, 7 technicians. We teach neurophysiology for medical undergraduates and for students in the Master and Ph.D. courses. Our research aims at elucidating cellular and molecular mechanisms underlying regulation of synaptic transmission and postnatal development of neuronal circuits.

Teaching activities

We teach neurophysiology for 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 sensori-motor 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 experiments of neurophysiology. First, students make intracellular recording from frog skeletal muscle fibers and examine the endplate potential for understanding basic properties of synaptic transmission. Second, students record 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 for discussing 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 the 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 mouse. We particularly focus on observing neuronal activities in real time in intact neurons. We use whole-cell patch clamp recording, calcium imaging, 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 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) Synaptic integration in intact animals:

To understand the physiological function of synapses *in vivo*, we analyze synaptic transmission and integration in single neurons in the intact brain by using *in vivo* two-photon imaging and whole-cell recording. We also develop new methods to implement these experiments.

References

(1) Tsujimura A, Kamae Y, Kawasaki H, Nagai H, Kano M, Tabata T. Carbon powder-filled microelectrode: An easy-to-fabricate probe for cellular electrochemistry. Anal Biochem. 2021 Sep 15;629:114316. doi: 10.1016/j.ab.2021.114316. Epub 2021 Jul 24.

(2) Lai ESK, Nakayama H, Miyazaki T, Nakazawa T, Tabuchi K, Hashimoto K, Watanabe M, Kano M. An autism-associated neuroligin-3 mutation affects developmental synapse elimination in the cerebellum. Front Neural Circuits. 2021 Jun 28;15:676891. doi: 10.3389/fncir.2021.676891. eCollection 2021.

(3) Toriumi K, Berto S, Koike S, Usui N, Dan T, Suzuki K, Miyashita M, Horiuchi Y, Yoshikawa A, Asakura M, Nagahama K, Lin HC, Sugaya Y, Watanabe T, Kano M, Ogasawara Y, Miyata T, Itokawa M, Konopka G, Arai M. Combined glyoxalase 1 dysfunction and vitamin B6 deficiency in a schizophrenia model system causes mitochondrial dysfunction in the prefrontal cortex. Redox Biol. 2021 Sep;45:102057. doi: 10.1016/j.redox.2021.102057. Epub 2021 Jun 24.

(4) Yamasaki M, Aiba A, Kano M, Watanabe M. mGluR1 signaling in cerebellar Purkinje cells: Subcellular organization and involvement in cerebellar function and disease. Neuropharmacology. 2021 Aug 15;194:108629. doi: 10.1016/j.neuropharm.2021.108629. Epub 2021 Jun 4.

(5) Song B, Kang CY, Han JH, Kano M, Konnerth A, Bae S. In vivo genome editing in single mammalian brain neurons through CRISPR-Cas9 and cytosine base editors. Comput Struct Biotechnol J. 2021 Apr 25;19:2477-2485. doi: 10.1016/j.csbj.2021.04.051. eCollection 2021.

(6) Nagahama K, Fujino S, Watanabe T, Uesaka N, Kano M. Combining electrophysiology and optogenetics for functional screening of pyramidal neurons in the mouse prefrontal cortex. STAR Protoc. 2021 Apr 15;2(2):100469. doi: 10.1016/j.xpro.2021.100469. eCollection 2021 Jun 18.

(7) Nagao S, Hirai H, Kano M, Yuzaki M. Masao Ito-A Visionary neuroscientist with a passion for the cerebellum. Neuroscience. 2021 May 10;462:1-3. doi: 10.1016/j.neuroscience.2021.02.028.

(8) Carrier-Ruiz A, Sugaya Y, Kumar D, Vergara P, Koyanagi I, Srinivasan S, Naoi T, Kano M, Sakaguchi M. Calcium imaging of adult-born neurons in freely moving mice. STAR Protoc. 2020 Dec 31;2(1):100238. doi: 10.1016/j.xpro.2020.100238. eCollection 2021 Mar 19.

Functional Biology

2. Pharmacology

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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 nano-scale 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. Aritake T, Hino H, Namiki S, Asanuma D, Hirose K, and Murata N. Fast and robust multiplane single molecule localization microscopy using deep neural network. ***Neurocomputing***, 451, 279-289 (2021)
2. Kitajima N, Takikawa K, Sekiya H, Asanuma D, Sakamoto H, Namiki S, Iino M and Hirose K. *In vivo* Fluorescence Imaging of Extracellular ATP in the Mouse Cerebral Cortex with a Hybrid-type Optical Sensor. ***Bio-protocol***, 11, e4046 (2021)
3. Takagi, T., Ueno, T., Ikawa, K., Asanuma, D., Nomura, Y., Uno, S., Komatsu, T., Kamiya, M., Hanaoka, K., Okimura, C., Iwadate, Y., Hirose, K., Nagano, T., Sugimura, K. & Urano, Y. Visualization and manipulation of actin cytoskeleton with small-molecular probes. ***Sci. Adv.*** 7(47), eabg8585 (2021).
4. Endo, Y., Asanuma, D., Namiki, S., Hirose, K., Uemura, A., Kubota, Y., & Miura, T. Quantitative modeling of regular retinal microglia distribution. ***Sci. Rep.*** 11, 22671 (2021).

Department of Systems Pharmacology

Professor

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Project Associate Professor

Yoichi Minami, Ph.D.

Full-time Lecturer

Koji L. Ode, Ph.D.

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Shoi Shi, Ph.D., Daisuke Tone, Ph.D.

Project Research Associate

Ningyuan Wang, Ph.D., 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), 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 through collaborative research.

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 spices 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 CaMKIIα/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, and allows for the integration of genetic factors (regulation by amino acid sequence) and environmental factors (post-translational modification of intracellular signaling pathways).

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 checkup" 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. Nojima S, Ishida S, Terayama K, Matsumoto K, Matsui T, Tahara S, Ohshima K, Kiyokawa H, Kido K, Ukon K, Yoshida SY, Mitani TT, Doki Y, Mizushima T, Okuno Y, Susaki EA, Ueda HR, Morii E. A Novel Three-Dimensional Imaging System Based on Polysaccharide Staining for Accurate Histopathologic Diagnosis of Inflammatory Bowel Diseases. Cell. Mol. Gastroenterol. Hepatol. online ahead of print
2. Glaser AK, Bishop KW, Barner LA, Susaki EA, Kubota SI, Gao G, Serafin RB, Balaram P, Turschak E, Nicovich PR, Lai H, Lucas LAG, Yi Y, Nichols EK, Huang H, Reder NP, Wilson JJ, Sivakumar R, Shamskhou E, Stoltzfus CR, Wei X,

Hempton AK, Pende M, Murawala P, Dodt HU, Imaizumi T, Shendure J, Beliveau BJ, Gerner MY, Xin L, Zhao H, True LD, Reid RC, Chandrashekar J, Ueda HR, Svoboda K, Liu JTC. A hybrid open-top light-sheet microscope for versatile multi-scale imaging of cleared tissues. Nat. Methods. 19, 613-619 (2022)

3. Chino H., Yamasaki A., Ode K.L., Ueda H.R., Noda N.N., Mizushima N. Phosphorylation by casein kinase 2 enhances the interaction between ER-phagy receptor. TEX264 and ATG8 proteins. EMBO Rep. 23, e54801 (2022)
4. Katori M., Shi S., Ode K.L., Tomita Y., Ueda H.R. The 103,200-arm acceleration dataset in the UK Biobank revealed a landscape of human sleep phenotypes. Proc. Natl. Acad. Sci. U.S.A. 119, e2116729119 (2022)
5. Yamada T., Shi S., Ueda H.R. A design principle of spindle oscillations in mammalian sleep. iScience 25, 103873 (2022)
6. Minami Y., Yuan Y., Ueda H.R. High-throughput Genetically Modified Animal Experiments Achieved by Next-generation Mammalian Genetics. J. Biol. Rhythms 37, 135-151 (2022)
7. Ode K.L., Shi S., Katori M., Mitsui K., Takanashi S., Oguchi R., Aoki D., Ueda H.R. A jerk-based algorithm ACCEL for the accurate classification of sleep–wake states from arm acceleration. iScience 25, 103727 (2022)
8. Sacconi L., Ueda H.R., Pagès S., Silvestri L. Fluorescence tissue microscopy. Prog. Biophys. Mol. Biol. 41, e110157 (2022)
9. Richardson D.S., Guan W., Matsumoto K., Pan C., Chung K., Ertürk A., Ueda H.R., Lichtman J.W. TISSUE CLEARING. Nat. Rev. Methods Primers 1, 84 (2021)
10. Minami Y., Yuan Y., Ueda H.R. Towards organism-level systems biology by next-generation genetics and whole-organ cell profiling. Biophys. Rev. 13, 1113-1126 (2021)
11. Watanabe-Takano H., Ochi H., Chiba A., Matsuo A., Kanai Y., Fukuhara S., Ito N., Sako K., Miyazaki T., Tainaka K., Harada I., Sato S., Sawada Y., Minamino N., Takeda S., Ueda H.R., Yasoda A., Mochizuki N. Mechanical load regulates bone growth via periosteal Osteocrin. Cell Rep. 1, 109380 (2021)

Pathology, Immunology and Microbiology

1. Pathology

Department of Pathology and Diagnostic Pathology

Professor

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Project Professor

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Associate Professor

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

Lecturer

Yoko Tateishi, M.D., Ph.D (~May 31)

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

Naoko Yamauchi, M.D., Ph.D. (~May 31, Hospital Lecturer)

Hirofumi Rokutan, M.D., Ph.D., Ryohei Kuroda, M.D., Ph.D. (Oct 1~), Masaki Suzuki, Munetoshi Hinata, M.D., Ph.D., Sho Yamazawa, M.D., Ph.D. (Department of Pathology, Hospital)

Naohiro Makise, M.D., Ph.D., Akiko Iwasaki, M.D., Ph.D., Mayu Hakozaki, M.D., Ph.D.

Yoichi Yasunaga, M.D., Ph.D. (~Nov 30, Project Research Associate, "Tsunagu"-Fukushima-Kanto Pathology- Forensic Pathology Cooperation Program, Dec 1~, Department of Pathology and Diagnostic Pathology)

Technical Support Specialist

Kei Sakuma, Kimiko Takeshita, M.T.

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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. Saito resigned on March 31, 2021. Drs. Suzuki (Department of Pathology, Hospital) and Hakozaki (Department of Pathology and Diagnostic Pathology) became research associates on Apr 1. Dr Yasunaga joined as a project research associate of "Tsunagu Program on Apr 1 (until Nov 2021, then moved to Department of Pathology and Diagnostic Pathology on Dec 1).

Ms. Kunita became a project lecturer Next-Generation Precision Medicine Development Laboratory on Apr 1, 2021.

Drs. Tateishi and Yamauchi moved to Yokohama Municipal Citizen’s Hospital and Asahi General Hospital, respectively, on May 30. Dr. Makise moved to Chiba Cancer Center on Sep 30. Dr. Kuroda became a research associate of the Department of Pathology (Hospital) on Oct 1.

Five postgraduate students (Kondo, Fukagawa, Usui, Urabe and Kuroe) finished the course and received Ph.D. In the new fiscal year, 2022, two 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. Saito, the 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.

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. Due to the COVID-19 pandemic, all of the courses and exercises were given online. Exercises of Systemic Pathology were conducted by using a web system which we established in 2020 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. Rokutan, Kuroda, Yamazawa and Iwasaki). 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, and pancreatobiliary cancers.

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

(Case reports are listed in the section of Department of Pathology)

1. Abe H, Kunita A, Otake Y, Kanda T, Kaneda A, Ushiku T, Fukayama M. Virus-host interactions in carcinogenesis of Epstein-Barr virus-associated gastric carcinoma: Potential roles of lost ARID1A expression in its early stage. PLoS One. 2021;16(9):e0256440.
2. Abe H, Ushiku T. Pathological diversity of gastric cancer from the viewpoint of background condition. Digestion. 2022;103:45-53.
3. Abe H, Yasunaga Y, Yamazawa S, Nakai Y, Gonoi W, Nishioka Y, Murono K, Sasaki K, Arita J, Kawai K, Nozawa H, Hasegawa K, Ishihara S, Ushiku T. Histological growth patterns of colorectal cancer liver metastases: a strong prognostic marker associated with invasive patterns of the primary tumor and p53 alteration. Hum Pathol. 2022;123:74-83.
4. Fujii Y, Sato Y, Suzuki H, Kakiuchi N, Yoshizato T, Lenis AT, Maekawa S, Yokoyama A, Takeuchi Y, Inoue Y, Ochi Y, Shiozawa Y, Aoki K, Yoshida K, Kataoka K, Nakagawa MM, Nannya Y, Makishima H, Miyakawa J, Kawai T, Morikawa T, Shiraishi Y, Chiba K, Tanaka H, Nagae G, Sanada M, Sugihara E, Sato TA, Nakagawa T, Fukayama M, Ushiku T, Aburatani H, Miyano S, Coleman JA, Homma Y, Solit DB, Kume H, Ogawa S. Molecular classification and diagnostics of upper urinary tract urothelial carcinoma. Cancer Cell. 2021;39(6):793-809.e8.
5. Hinata M, Ushiku T. Detecting immunotherapy-sensitive subtype in gastric cancer using histologic image-based deep learning. Scientific Reports. 2021;11(1):22636.
6. Imai S, Ooki T, Murata-Kamiya N, Komura D, Tahmina K, Wu W, Takahashi-Kanemitsu A, Knight CT, Kunita A, Suzuki N, Del Valle AA, Tsuboi M, Hata M, Hayakawa Y, Ohnishi N, Ueda K, Fukayama M, Ushiku T, Ishikawa S, Hatakeyama M. Helicobacter pylori CagA elicits BRCAness to induce genome instability that may underlie bacterial gastric carcinogenesis. Cell Host Microbe. 2021;29(6):941-958.e10.
7. Iwasaki A, Shinozaki-Ushiku A, Kunita A, Yamazawa S, Sato Y, Yamashita H, Fukayama M, Seto Y, Ushiku T. Human Leukocyte Antigen Class I Deficiency in Gastric Carcinoma: An Adaptive Immune Evasion Strategy Most Common in Microsatellite Instable Tumors. Am J Surg Pathol. 2021;45(9):1213-1220.
8. Kashima J, Hishima T, Okuma Y, Horio H, Ogawa M, Hayashi Y, Horiguchi SI, Motoi T, Ushiku T, Fukayama M. CD70 in Thymic Squamous Cell Carcinoma: Potential Diagnostic Markers and Immunotherapeutic Targets. Front Oncol. 2022;11:808396.
9. Komura D, Kawabe A, Fukuta K, Sano K, Umezaki T, Koda H, Suzuki R, Tominaga K, Ochi M, Konishi H, Masakado F, Saito N, Sato Y, Onoyama T, Nishida S, Furuya G, Katoh H, Yamashita H, Kakimi K, Seto Y, Ushiku T, Fukayama M, Ishikawa S. Universal encoding of pan-cancer histology by deep texture representations. Cell Rep. 2022;38(9):110424.
10. Kudo N, Kudoh S, Matsuo A, Motooka Y, Ito T. ZMYM3 may promote cell proliferation in small cell lung carcinoma. Acta Histochem Cytochem. 2021;54(5):143–153.
11. Kuroe T, Watanabe R, Kojima M, Morisue R, Sugano M, Kuwata T, Masuda H, Kusuhara S, Matsubara N, Oda S, Ushiku T, Ishii G. Evaluation of the morphological features and

unfavorable prognostic impact of dirty necrosis in renal cell carcinoma. J Cancer Res Clin Oncol. 2021;147(4):1089-1100.

12. Shi C, Badgwell B, Gibson MK, Grabsch HI, Hong S, Kumarasinghe P, Lam A, Lauwers G, O'Donovan M, Tang L, Ushiku T, van der Post C, Vieth M, Nagtegaal ID (2021). Carcinoma of the Stomach Histopathology Reporting Guide, 2nd edition. International Collaboration on Cancer Reporting; Sydney, Australia.
13. Shi C, Badgwell BD, Grabsch HI, Gibson MK, Hong SM, Kumarasinghe P, Lam AK, Lauwers G, O'Donovan M, van der Post RS, Tang L, Ushiku T, Vieth M, Selinger CI, Webster F, Nagtegaal ID. Data Set for Reporting Carcinoma of the Stomach in Gastrectomy. Arch Pathol Lab Med. 2021; Epub ahead of print.
14. Shi C, Bourke M, Hong S, Kumarasinghe P, Lam A, Lauwers G, O'Donovan M, Ushiku T, van der Post C, Vieth M, Nagtegaal ID (2021). Endoscopic Resection of the Stomach Histopathology Reporting Guide, 2nd edition. International Collaboration on Cancer Reporting; Sydney, Australia.
15. Taguchi J, Shibata H, Kabata M, Kato M, Fukuda K, Tanaka A, Ohta S, Ukai T, Mitsunaga K, Yamada Y, Nagaoka SI, Yamazawa S, Ohnishi K, Woltjen K, Ushiku T, Ozawa M, Saitou M, Shinkai Y, Yamamoto T, Yamada Y. DMRT1-mediated reprogramming drives development of cancer resembling human germ cell tumors with features of totipotency. Nat Commun. 2021; 12(1):5041.
16. Yachida S, Totoki Y, Noë M, Nakatani Y, Horie M, Kawasaki K, Nakamura H, Saito-Adachi M, Suzuki M, Takai E, Hama N, Higuchi R, Hirono S, Shiba S, Kato M, Furukawa E, Arai Y, Rokutan H, Hashimoto T, Mitsunaga S, Kanda M, Tanaka H, Takata S, Shimomura A, Oshima M, Hackeng WM, Okumura T, Okano K, Yamamoto M, Yamaue H, Morizane C, Arihiro K, Furukawa T, Sato T, Kiyono T, Brosens LAA, Wood LD, Hruban RH, Shibata T. Comprehensive Genomic Profiling of Neuroendocrine Carcinomas of the Gastrointestinal System. Cancer Discov. 2022; 12(3);692-711.
17. Yamazawa S, Ushiku T. Carcinosarcoma of the stomach: four cases that expand the morphologic spectrum of gastric cancer with a primitive phenotype. Virchows Arch. 2022;480(5):1051-1062.
18. Zhang CD, Takeshima H, Sekine S, Yamashita S, Liu YY, Hattori N, Abe H, Yamashita H, Fukuda M, Imamura Y, Ushiku T, Katai H, Makino H, Watanabe M, Seto Y, Ushijima T. Prediction of tissue origin of adenocarcinomas in the esophagogastric junction by DNA methylation. Gastric Cancer. 2022;25(2):336-345.

Department of Molecular Pathology

Professor

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Associate Professors

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Shogo Ehata, M.D., Ph.D. (Environmental Science Center, until September 2021)

Assistant Professors

Masato Morikawa, M.D., Ph.D.

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Introduction and organization

Our department has a more than 120-year history from its establishment as the Department of Pathology. Kohei Miyazono is Professor of the Department of Molecular Pathology from August 2000. At the end of March 2021, he retired from his position. In March 2021, the Department consists of a professor, an associate professor, an assistant professor, technical assistants, and some research fellows, including three graduate students, and a post-doctoral fellow.

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 very important for medical students to study basic oncology, we teach basic tumor biology in our lectures of General Pathology. All lecture courses were conducted online in 2021. In addition, we offer several laboratory courses for students from molecular pathological points of view.

We also supervise research activities of the graduate students of the Department. Our laboratory is located at the 11th floor at the Research Building of Graduate School of Medicine. The laboratory is very convenient for doing research, because most of the experiments can be done on this floor. We have "Progress Meeting" once a month and "Monday Seminar" once a month. We have been collaborating with Prof. Carl-Henrik Heldin's group, Uppsala University, Sweden for more than 25 years.

From 2018, World-leading INnovative Graduate School Program for Life Science and Technology (WINGS-LST) has started and one of our graduate students is supported by this program. This program will stimulate interaction between students and scientists in the program as well as those from other laboratories (square.umin.ac.jp/wings-lf/). In addition, Fostering Advanced Human Resources to Lead Green Transformation (GX) project started from 2021, and another student is supported by this program.

Research activities

Our major research interest is to elucidate how members of the TGF-β (transforming growth factor-β) family transduce signals, and how they regulate growth, differentiation, and apoptosis of various cells.

From 2017, our research is mainly supported by a Grant-in-Aid for Scientific Research on Innovative Area on Integrated Analysis and Regulation of

Cellular Diversity (17H06326) from MEXT. From 2020, our research is also supported by a Grant-in-Aid for Scientific Research (A) on “Comprehensive studies on the mechanisms of cancer metastasis from molecular signaling to whole-body level” (20H00513) from the Japanese Society for the Promotion of Science (JSPS). From 2021, our new project on a new strategy for treatment of the mesenchymal type of glioblastoma is accepted (21ck0106705h0001) by the Practical Research for Innovative Cancer Control Program of Japan Agency for Medical Research and Development (AMED).

Followings are some research results obtained at our laboratory in 2021.

1) *Monovalent follistatin-like-3 (mono-FSTL3)-Fc-fusion protein increases muscle mass in mice.*

Inhibition of some TGF-β family ligands, including growth differentiation factor 8 (GDF8, also known as myostatin) and activin A, is expected to induce muscle growth in the elderly and in patients. We studied the effects of an endogenous antagonist against TGF-β family ligands, follistatin-like 3 (FSTL3), which binds and neutralizes activins, GDF8/myostatin, and GDF11, but not TGF-βs or bone morphogenetic proteins (BMPs). Although bivalent human FSTL3 Fc-fusion protein was rapidly cleared from mouse circulation, monovalent FSTL3-Fc (mono-FSTL3-Fc) generated with the knobs-into-holes technology showed significantly longer serum half-life in mice. Systemic administration of mono-FSTL3-Fc in mice induced muscle fiber hypertrophy and increased muscle mass. Our results thus suggest that the monovalent FSTL3-based therapy overcomes the difficulties of current anti-GDF8 therapies (Ozawa et al. iScience 2021).

2) *Visualization of the cancer cell cycle by tissue-clearing technology using the Fucci reporter system.*

Tissue-clearing technology is an imaging technique currently utilized not only in neuroscience research but also in cancer research. In our previous studies, we used tissue-clearing methods for the detection of metastatic tumors. In the present study, we showed that the cell cycles of primary and metastatic tumors were visualized by tissue-clearing methods using some cancer cell lines (human lung adenocarcinoma A549 and mouse breast cancer 4T1), stably expressing fluorescent ubiquitination-based cell cycle indicator (Fucci) reporter. Interestingly, fluorescence patterns of the Fucci reporter of tumor colonies were different between various organs, and even among colonies in the same organs. The effects of anti-tumor drugs were also analyzed using these Fucci reporter cells. We found that, of the three anti-tumor drugs studied, 5-fluorouracil (5-FU) treatment on 4T1-Fucci cells resulted in characteristic fluorescent patterns by the induction of G2/M arrest in vitro as well as in vivo. Thus, the combination of a tissue-clearing method with the Fucci reporter may be useful for analyzing the mechanisms of cancer metastasis and drug resistance (Takahashi et al. Cancer Sci 2021).

3) *Suppression of anti-pyroptotic function of TGF-β by a synthetic dsRNA analogue in triple negative breast cancer (TNBC) cells.*

Transfection of polyI:C, a conventionally used synthetic double-stranded RNA (dsRNA) analogue, activates retinoic acid-inducible gene-I (RIG-I)-like receptors (RLRs), and has been evaluated in clinical trials. However, mechanisms of tumor suppression by RLRs, including interactions with other signaling pathways, remain to be elucidated. We found that transfection of polyI:C in cells suppressed TGF-β signaling in an RLR-dependent manner. Suppression of TGF-β signaling by polyI:C promoted cancer cell death, which was attenuated by forced expression of constitutively active Smad3. Interestingly, cell death by polyI:C transfection exhibited characteristics of pyroptosis, which is distinct from apoptosis. Therapeutic efficacy of polyI:C transfection was also confirmed using a mouse model. These findings suggest that intratumor administration of polyI:C and related dsRNA analogues may be an interesting strategy for treatment of TNBC through inhibition of the anti-pyroptotic function of TGF-β (Tamura et al. Mol Oncol 2021).

4) *Heterogeneity of endoglin expression in clear cell renal cell carcinoma (ccRCC) and its relationship to the tumor microenvironment.*

Intratumoral heterogeneity is a potential cause of drug resistance and metastatic cancer progression.

Although endoglin (ENG, also known as CD105) has been proposed as a marker for cancer-initiating cells in ccRCC, we found that ENG-positive population did not enrich other cancer-initiating cell markers or induce the differentiation into the ENG-negative population in our experimental systems. Mouse tumor inoculation models revealed that the tumor-forming capabilities of ENG-positive and ENG-negative cells in vivo appeared to be dependent on the tumor microenvironment, with the renal microenvironment most preferable to ENG-positive cells. Thus, the renal microenvironment, rather than the ENG-positive cell-centered hierarchy, maintains cellular heterogeneity in ccRCC (Momoi et al. Cancer Sci 2021).

References

1. Takahashi, K., Ehata, S., Miyauchi, K., Morishita, Y., Miyazawa, K., and Miyazono, K. (2021) Neurotensin receptor 1 signaling promotes pancreatic cancer progression. ***Molecular Oncology*** 15 (1), 151-166. doi: 10.1002/1878-0261.12815.
2. Kok, S.Y., Oshima, H., Takahashi, K., Nakayama, M., Murakami, K., Ueda, H.R., Miyazono, K., and Oshima, M. (2021) Malignant subclone drives metastasis of genetically and phenotypically heterogenous cell clusters through fibrotic niche generation. ***Nature Communications*** 12 (1), 863. doi: 10.1038/s41467-021-21160-0.
3. Kubota, S.I., Takahashi, K., Mano, T., Matsumoto, K., Katsumata, T., Shi, S., Tainaka, K., Ueda, H.R., Ehata, S., and Miyazono, K. (2021) Whole-organ analysis of TGF-β-mediated remodelling of the tumour microenvironment by tissue clearing. ***Communications Biology*** 4 (1), 294. doi: 10. 1038/s42003-021-01786-y.
4. Sakamoto, K., Endo, K., Sakamoto, K., Kayamori, K., Ehata, S., Ichikawa, J., Ando, T., Nakamura, R., Kimura, Y., Yoshizawa, K., Masuyama, K., Kawataki, T., Miyake, K., Ishii, H., Kawasaki, T., Miyazawa, K., and Saitoh, M. (2021) EHF suppresses cancer progression by inhibiting ETS1-mediated ZEB expression. ***Oncogenesis*** 10 (3), 26. doi: 10.1038/s41389-021-00313-2.
5. Katsuno, Y. and Derynck, R. (2021) Epithelial plasticity, epithelial-mesenchymal transition, and the TGF-β family. ***Developmental Cell*** 56 (6), 726-746. doi: 10.1016/j.devcel.2021.02.028.
6. Tamura, Y., Morikawa, M., Tanabe, R., Miyazono, K., and Koinuma, D. (2021) Anti-pyroptotic function of TGF-β is suppressed by a synthetic dsRNA analogue in triple negative breast cancer cells. ***Molecular Oncology*** 15 (5), 1289-1307. doi: 10.1002/1878-0261.12890.
7. Ozawa, T., Morikawa, M., Morishita, Y., Ogikubo, K., Itoh, F., Koinuma, D., Nygren, P.Å., and Miyazono, K. (2021) Systemic administration of monovalent follistatin-like-3-Fc-fusion protein increases muscle mass in mice. ***iScience*** 24 (5), 102488. doi: 10.1016/j.isci.2021.102488.
8. Yamamoto, H., Sakai, N., Ohte, S., Sato, T., Sekimata, K., Matsumoto, T., Nakamura, K., Watanabe, H., Mishima-Tsumagari, C., Tanaka, A., Hashizume, Y., Honma, T., Katagiri, T., Miyazono, K., Tomoda, H., Shirouzu, M., and Koyama, H. (2021) Novel bicyclic pyrazoles as potent ALK2 (R206H) inhibitors for the treatment of fibrodysplasia ossificans progressiva. ***Bioorganic & Medicinal Chemistry Letters*** 38, 127858. doi: 10.1016/j.bmcl.2021.127858.
9. Motizuki, M., Koinuma, D., Yokoyama, T., Itoh, Y., Omata, C., Miyazono, K., Saitoh, M., and Miyazawa, K. (2021) TGF-β-induced cell motility requires down-regulation of ARHGAPs to sustain Rac1 activity. ***Journal of Biological Chemistry*** 296, 100545. doi: 10.1016/j.jbc.2021.100545.
10. Fukuda, T., Fukuda, R., Miyazono, K., and Heldin, C.-H. (2021) Tumor promoting effect of BMP signaling in endometrial cancer. ***International Journal of Molecular Sciences*** 22 (15), 7882. doi: 10.3390/ijms22157882.
11. Momoi, Y., Nishida, J., Miyakuni, K., Kuroda, M., Kubota, S.I., Miyazono, K., and Ehata, S. (2021) Heterogenous expression of endoglin marks advanced renal cancer with distinct tumor microenvironment fitness. ***Cancer Science*** 112 (8), 3136-3149. doi: 10.1111/cas.15007.

12. Takahashi, K., Tanabe, R., Ehata, S., Kubota, S.I., Morishita, Y., Ueda, H.R., and Miyazono, K. (2021) Visualization of the cancer cell cycle by tissue-clearing technology using the Fucci reporter system. ***Cancer Science*** 112 (9), 3796-3809. doi: 10.1111/cas.15034.
13. Fukuda, T., Fukuda, R., Koinuma, D., Moustakas, A., Miyazono, K., and Heldin, C.-H. (2021) BMP2-induction of FN14 promotes protumorigenic signaling in gynecologic cancer cells. ***Cellular Signalling*** 87, 100146. doi: 10.1016/j.cellsig.2021.110146.
14. Ozawa, T., Miyazono, K., and Morikawa, M. (2021) Preparation of monovalent follistatin-like 3-Fc-fusion protein and evaluation of its effects on muscle mass in mice. ***STAR Protocols*** 2 (4), 100839. doi: 10.1016/j.xpro.2021.100839.

Pathology, Immunology and Microbiology

2. Microbiology

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Introduction and Organization

Professor emeritus Akio Nomoto who had been the chief of the Department retired in 2008 and moved to Microbial Chemistry Research Foundation as the Chairman of Board. From 2009, new Department of Microbiology started with Professor Masanori Hatakeyama as the new chief. The present Department consists of 16 members; 1 professor (Dr. Hatakeyama), 1 senior lecturer (Dr. Kamiya), 2 research associates (Drs. Kanemitsu and Hayashi), 3 post-doctoral fellows (Drs. Nishikawa, Kikuchi, and Ooki), 2 academic assistants (Ms. Sakamoto and Komatsu), 7 graduate school students (Mr. and Ms. Wada, Imai, Tahmina, Wu, Priscillia, Del Valle Lazarte, Shrestha).

Education

In a series of lectures (totally 64 hr) and laboratory courses (36 hr), the following subjects 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) Application of microbial organisms for bio-technology
6) Socioeconomic impact of microbial diseases

Research

Gastric cancer is the third leading cause (10.4%) of cancer death worldwide. It has now been well established that infection with *Helicobacter pylori* (*H. pylori*) is associated with the development of gastric cancer. Especially, infection with *H. pylori* strains carrying a gene called *cagA* plays an essential role in gastric carcinogenesis. The *cagA*-positive *H. pylori* delivers the *cagA* gene product, the CagA protein, into the host gastric epithelial cells via the type IV secretion system. Through a series of studies, we have uncovered the molecular mechanisms by which delivered CagA causes transformation of gastric epithelial cells.

East Asian countries such as Japan, Korea and China, are known to show the highest incidence of gastric cancer in the world. In Japan, for instance, more than 40,000 peoples are killed by gastric cancer each year. Thus, establishment of new strategies for prevention and treatment for gastric cancer is urgently required. In our department, we are conducting cutting-edge researches, ranging from molecular structural biology to mouse genetics, to elucidate oncogenic mechanisms of the bacterial CagA protein. These researches will provide an opportunity to develop molecular-targeting methods that effectively prevent the development of gastric cancer. We made substantial progress in the following research during the current year.

1. *Helicobacter pylori* CagA elicits BRCAness to induce genome instability that may underlie bacterial gastric carcinogenesis

Chronic infection with *cagA*-positive *H. pylori* plays a critical role in the development of gastric cancer. However, once established, *H. pylori* is not required for the maintenance of cancer cells, indicating that CagA-dependent carcinogenesis proceeds through a "hit-and-run" mechanism.

The CagA protein, encoded by the *cagA* gene, is directly injected into gastric epithelial cells through the type IV secretion system (T4SS). Inside the host cells, CagA binds and inhibits the polarity-regulating serine/threonine kinase PAR1b (also known as MARK2) via CM motif, thereby causing junctional and polarity defects. In this study, we found that CagA impairs nuclear accumulation of BRCA1 in a CM motif-dependent manner. Mechanistically, CagA/PAR1b interaction inactivates PAR1b and thereby inhibits PAR1b-dependent phosphorylation of BRCA1 on Ser616 that is required for cytoplasmic-to-nuclear translocation of BRCA1. The breast/ovarian tumor suppressor BRCA1 that has essential functions in homologous recombination (HR), a high-fidelity mechanism to repair DNA double-strand breaks (DSBs), is also important in the protection of stalled replication forks. CagA-induced shortage of nuclear BRCA1 causes replication fork instability leading to DSBs that are repaired through error-prone pathways such as non-homologous end joining (NHEJ). The CagA/PAR1b interaction also stimulates Hippo signaling and thereby circumvents DSB-triggered apoptosis. However, despite successful escape from apoptosis, CagA-induced DSBs activate p53-$p21^{Cip1}$ axis to inhibit cell proliferation. It has been reported that *TP53* is the most frequently mutated gene in gastric cancer. Indeed, p53 inactivation allows the proliferation of CagA-delivered cells. Furthermore, intermittent expression of CagA in *TP53*-mutant cells, which mimics CagA delivery in the *H. pylori*-colonized human stomach, induces somatic mutations with BRCAness-associated COSMIC signatures, AC3 and ID6, indicating that CagA elicits transient BRCAness. Genome instability caused by CagA-induced transient BRCAness may promote acquisition of additional driver gene mutations that confer *H. pylori*-independence in terms of neoplastic transformation. This study revealed the molecular mechanism by which *H. pylori* CagA promotes "hit-and-run" gastric carcinogenesis.

2. Mouse gastric epithelial cells resist CagA delivery by the *Helicobacter pylori* typeIV secretion system

Most if not all human gastric cancers are caused by chronic infection of the stomach lining with *H. pylori* strains that possess the *cagA* gene. Inside the host cells, CagA undergoes tyrosine phosphorylation by Src family kinases (SFKs) or c-Abl kinase. Tyrosine-phosphorylated CagA binds to and aberrantly activates pro-oncogenic tyrosine phosphatase SHP2, thereby causing aberrant activation of the RAS-ERK kinase signaling pathway. CagA-dependent SHP2 deregulation and PAR1b inhibition contribute to the neoplastic transformation of CagA-delivered gastric epithelial cells.

Mice have been used in many studies for *H. pylori*-dependent gastric diseases. Infection of mice with *cagA*-positive *H. pylori* strains induced more severe gastritis than infection with *cagA*-negative strains did. However, even long-term infection of mice with *cagA*-positive strains did not induce gastric cancer. In contrast, transgenic expression of CagA in mice gave rise to spontaneous gastrointestinal and hematological malignancies. These findings raise the possibility that *cagA*-positive *H. pylori* cannot efficiently deliver CagA into mouse gastric epithelial cells.

The initial step in *H. pylori* infection is adherence of *H. pylori* to the human gastric epithelial cells. *H. pylori* exploits the interaction of bacterial adhesin protein HopQ with human epithelial CEACAMs (CEACAM1, 5, and 6) to stably adhere to gastric epithelial cells, which is necessary for delivery of the *H. pylori* CagA oncoprotein into the epithelial cells via a type IV secretion system. In contrast to human CEACAMs, however, HopQ does not interact with Ceacam1 (mouse CEACAM1) in vitro or in CHO cells ectopically expressing Ceacam1. Since the mouse genome lacks *Ceacam5* and *Ceacam6*, no significant HopQ-Ceacam interaction may occur in mouse gastric epithelial cells. Here, we found that the mouse stomach has a much lower expression level of Ceacam1 than the expression level of CEACAM1 in

the human stomach using a public database (NCBI Gene). Consistently, mouse gastric epithelial cells resist CagA delivery by *cagA*-positive *H. pylori*. We established human CEACAM (CEACAM1, 5, or 6)-expressing mouse gastric epithelial cells. CagA delivery was restored by ectopic expression of human CEACAM1 or CEACAM5 in mouse gastric epithelial cells. In contrast, despite sufficient expression of human CEACAM6 on the mouse gastric epithelial cells, there was no evidence for CagA delivery. Thus, although mice are routinely used for *H. pylori* infection studies, a low expression level of Ceacam1 in the mouse stomach together with the loss or greatly reduced interaction of HopQ with Ceacams make the mouse an inappropriate model for studying the role of *H. pylori*-delivered CagA in gastric pathogenesis, including the development of gastric cancer.

Publications

1. Tahmina, K., Hikawa, N., Takahashi-Kanemitsu, A., Knight, C.T., Sato, K., Itoh, F., Hatakeyama, M. Transgenically expressed *Helicobacter pylori* CagA in vascular endothelial cells accelerates arteriosclerosis in mice. *Biochem. Biophys. Res. Commun.* in press.
2. Nishikawa, H., Christiany, P., Hayashi, T., Iizasa, H., Yoshiyama, H., Hatakeyama, M. Kinase activity of PAR1b, which mediates nuclear translocalization of the BRCA1 tumor suppressor, is potentiated by nucleic acid-mediated PAR1b multimerization. *Int. J. Mol. Sci.* in press.
3. Murata-Kamiya, N., Hatakeyama, M. *Helicobacter pylori*-induced DNA double-stranded break in the development of gastric cancer. *Cancer Sci.* in press.
4. Shrestha, R., Murata-Kamiya, N., Imai, S., Yamamoto, M., Tsukamoto, T., Nomura, S., Hatakeyama, M. Mouse gastric epithelial cells resist CagA delivery by the *Helicobacter pylori* type IV secretion system. *Int. J. Mol. Sci.* **23**(5): 2492 (2021)
5. Kolinjivadi, A.M., Sankar, H., Choudhary, R., Tay, L.S., Tan, T.Z., Murata-Kamiya, N., Voon, D.C., Kappei, D., Hatakeyama, M., Krishnan, V., Ito, Y. The *H. pylori* CagA oncoprotein induces DNA double strand breaks through Fanconi Anemia pathway downregulation and replication fork collapse. *Int. J. Mol. Sci.* **23**(3): 1661 (2021)
6. Imai, S., Ooki, T., Murata-Kamiya, N., Komura, D., Tahmina, K., Wu, W., Takahashi-Kanemitsu, A., Knight, C.T., Kunita, A., Suzuki, N., Tsuboi, M., Hata, M., Hayakawa, Y., Ohnishi, N., Ueda, K., Fukayama, M., Ushiku, T., Ishikawa, S., Hatakeyama, M. *Helicobacter pylori* CagA elicits BRCAness to induce genome instability that may underlie bacterial gastric carcinogenesis. *Cell Host Microbe*, **29**(6): 941-958 (2021)
7. Ooki, T., Hatakeyama, M. Protocol for visualizing conditional interaction between transmembrane and cytoplasmic proteins. *STAR Protocols* **2:** 100430 (2021)

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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 l, 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

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) Molecular pathogenesis of hepatocellular carcinoma in HCV infection
4) Pathogenesis of progression of HIV infection
5) Molecular pathogenesis of the mitochondrial disturbances in viral infections
6) Molecular pathogenesis of hepatitis B viral infection
7) Host defenses to microorganisms
8) Molecular analysis of innate immunity in microorganism infection
9) New detection method and pathogenesis of opportunistic cytomegaloviral infection
10) Mechanisms and molecular epidemiology of multi-drug resistant microorganisms
11) Epidemiology of *Clostridioides difficile* infection
12) Clinical characteristics and molecular epidemiology of hypervirulent *Klebsiella pnemoniae* infection

Publications

1. Ito H, Okamoto K, Yamamoto S, Yamashita M, Kanno Y, Jubishi D, Ikeda M, Harada S, Okugawa S, Moriya K. Incidence and Risk Factors for Inappropriate Use of Non-Culture-Based Fungal Assays: Implication for Diagnostic Stewardship. Open Forum Infect Dis. 2021 Dec 6;9(1):ofab601.
2. Yokoyama R, Kurano M, Nakano Y, Morita Y, Ohmiya H, Kishi Y, Okada J, Qian C, Xia F, He F, Zheng L, Yu Y, Mizoguchi M, Higurashi Y, Harada S, Jubishi D, Okamoto K, Moriya K, Kodama T, Yatomi Y. Association of the Serum Levels of the Nucleocapsid Antigen of SARS-CoV-2 With the Diagnosis, Disease Severity, and Antibody Titers in Patients With COVID-19: A Retrospective Cross-Sectional Study. Front Microbiol. 2021 Dec 9;12:791489.
3. Kobayashi T, Ikeda M, Okada Y, Higurashi Y, Okugawa S, Moriya K. Clinical and Microbiological Characteristics of Recurrent Escherichia coli Bacteremia. Microbiol Spectr. 2021 Dec 22;9(3):e0139921.
4. Nomura Y, Okamoto K, Ohama Y, Higurashi Y, Harada S, Moriya K. Tenosynovitis caused by Mycobacterium marseillense, initially identified as Mycobacterium avium complex using AccuProbe and COBAS TaqMan. BMC Infect Dis. 2021 Oct 23;21(1):1092.
5. Ohama Y, Aoki K, Harada S, Nagasawa T, Sawabe T, Nonaka L, Moriya K, Ishii Y, Tateda K. Genetic Environment Surrounding $bla_{OXA-55-like}$ in Clinical Isolates of Shewanella algae Clade and Enhanced Expression of $bla_{OXA-55-like}$ in a Carbapenem-Resistant Isolate. mSphere. 2021 Oct 27;6(5):e0059321.
6. Kobayashi T, Ikeda M, Ohama Y, Murono K, Ikeuchi K, Kitaura S, Okamoto K, Okugawa S, Ishihara S, Moriya K. First human case of catheter-related blood stream infection caused by Staphylococcus schleiferi subspecies coagulans: a case report and literature review. Ann Clin Microbiol Antimicrob. 2021 Sep 25;20(1):68.
7. Minami T, Tateishi R, Fujiwara N, Nakagomi R, Nakatsuka T, Sato M, Uchino K, Enooku K, Nakagawa H, Fujinaga H, Izumiya M, Hanajiri K, Asaoka Y, Kondo Y, Tanaka Y, Otsuka M, Ohki T, Arai M, Tanaka A, Yasuda K, Miura H, Ogata I, Kamoshida T, Inoue K, Koike Y, Akamatsu M, Mitsui H, Fujie H, Ogura K, Yoshida H, Wada T, Kurai K, Maekawa H, Obi S, Teratani T, Masaki N, Nagashima K, Ishikawa T, Kato N, Moriya K, Yotsuyanagi H, Koike K. Impact of Obesity and Heavy Alcohol Consumption on Hepatocellular Carcinoma Development after HCV Eradication with Antivirals. Liver Cancer. 2021 Jul;10(4): 309-319.

8. Shinohara T, Okamoto K, Koyano S, Otani A, Yamashita M, Wakimoto Y, Jubishi D, Hashimoto H, Ikeda M, Harada S, Okugawa S, Moriya K. Plesiomonas shigelloides Septic Shock Following Ingestion of Dojo Nabe (Loach Hotpot). Open Forum Infect Dis. 2021 Jul 26; 8(8):ofab401.
9. Kurokawa R, Inui S, Gonoi W, Nakai Y, Ishida M, Watanabe Y, Kubo T, Amano Y, Okamoto K, Kage H, Harada S, Tanaka G, Kawahara T, Nagase T, Moriya K, Abe O. Standardized reporting systems of chest computed tomography in a population with low coronavirus disease 2019 prevalence: A retrospective comparative study. Heliyon. 2021 Aug;7(8):e07743.
10. Sato Y, Atarashi K, Plichta DR, Arai Y, Sasajima S, Kearney SM, Suda W, Takeshita K, Sasaki T, Okamoto S, Skelly AN, Okamura Y, Vlamakis H, Li Y, Tanoue T, Takei H, Nittono H, Narushima S, Irie J, Itoh H, Moriya K, Sugiura Y, Suematsu M, Moritoki N, Shibata S, Littman DR, Fischbach MA, Uwamino Y, Inoue T, Honda A, Hattori M, Murai T, Xavier RJ, Hirose N, Honda K. Novel bile acid biosynthetic pathways are enriched in the microbiome of centenarians. Nature. 2021 Nov;599(7885):458-464.
11. Shimura T, Kurano M, Okamoto K, Jubishi D, Kano K, Igarashi K, Shimamoto S, Aoki J, Moriya K, Yatomi Y. Increase in serum levels of phosphatidylserine-specific phospholipase A_1 in COVID-19 patients. Cell Mol Immunol. 2021 Sep;18(9):2275-2277.
12. Hangai S, Kawamura T, Kimura Y, Chang CY, Hibino S, Yamamoto D, Nakai Y, Tateishi R, Oshima M, Oshima H, Kodama T, Moriya K, Koike K, Yanai H, Taniguchi T. Orchestration of myeloid-derived suppressor cells in the tumor microenvironment by ubiquitous cellular protein TCTP released by tumor cells. Nat Immunol. 2021 Aug;22(8):947-957.
13. Mizoguchi M, Harada S, Okamoto K, Higurashi Y, Ikeda M, Moriya K. Comparative performance and cycle threshold values of 10 nucleic acid amplification tests for SARS-CoV-2 on clinical samples. PLoS One. 2021 Jun 23;16(6): e0252757.
14. Nishikawa H, Shiraki M, Hiramatsu A, Hara N, Moriya K, Hino K, Koike K. Reduced handgrip strength predicts poorer survival in chronic liver diseases: A large multicenter study in Japan. Hepatol Res. 2021 Sep;51(9):957-967.
15. Ikeda M, Wakabayashi Y, Okamoto K, Yanagimoto S, Okugawa S, Moriya K. Changing trends in lipid profile and biomarkers of renal function and bone metabolism before and after switching from tenofovir disoproxil fumarate to tenofovir alafenamide: a prospective observational study. AIDS Res Ther. 2021 May 27;18(1):30.
16. Hirano J, Yoshio S, Sakai Y, Songling L, Suzuki T, Itoh Y, Zhang H, Chen DV, Haga S, Oomori H, Kodama T, Maeda Y, Ono Y, Takahashi Y, Standley DM, Yamamoto M, Moriishi K, Moriya K, Kanto T, Takehara T, Koike K, Matsuura Y, Okamoto T. Hepatitis C virus modulates signal peptide peptidase to alter host protein processing. Proc Natl Acad Sci U S A. 2021 Jun 1;118(22): e2026184118.
17. Ikeda M, Kobayashi T, Fujimoto F, Okada Y, Higurashi Y, Tatsuno K, Okugawa S, Moriya K. The prevalence of the iutA and ibeA genes in Escherichia coli isolates from severe and non-severe patients with bacteremic acute biliary tract infection is significantly different. Gut Pathog. 2021 May 18;13(1):32.
18. Okushin K, Suzuki R, Tsutsumi T, Okamoto K, Ikeuchi K, Kado A, Minatsuki C, Minami-Kobayashi Y, Satoh N, Ikeda M, Harada S, Enooku K, Fujinaga H, Yotsuyanagi H, Koike K, Moriya K. Change in hepatitis C virus positivity among needle-stick injury source patients: a 10-year experience in a Japanese tertiary hospital. BMC Infect Dis. 2021 Apr 30;21(1):399.
19. Amano Y, Kage H, Tanaka G, Gonoi W, Nakai Y, Kurokawa R, Inui S, Okamoto K, Harada S, Iwabu M, Morizaki Y, Abe O, Moriya K, Nagase T. Diagnostic prediction of COVID-19 based on clinical and radiological findings in a relatively low COVID-19 prevalence area. Respir Investig. 2021 Jul;59(4):446-453.
20. Oyama Y, Yasunaga M, Honda A, Maki H, Masamoto Y, Kobayashi T, Wakabayashi Y, Okugawa S, Moriya K, Kurokawa M. Severe cellulitis caused by Achromobacter xylosoxidans

after allogeneic hematopoietic stem cell transplantation. J Infect Chemother. 2021 May; 27(5):770-772.

21. Ikeuchi K, Okamoto K, Inoue N, Okugawa S, Moriya K. Chronic Disseminated Gonococcal Infection in a Japanese Man with Novel C5 Gene Mutation. J Clin Immunol. 2021 Apr;41(3):691-693.
22. Ishihara Y, Okamoto K, Shimosaka H, Ono Y, Kanno Y, Ikeda M, Harada S, Kurano M, Okugawa S, Moriya K, Yatomi Y. Prevalence and clinical characteristics of patients with biologically false-positive reactions with serological syphilis testing in contemporary practice: 10-year experience at a tertiary academic hospital. Sex Transm Infect. 2021 Sep; 97(6):397-401.
23. Osawa I, Okamoto K, Ikeda M, Otani A, Wakimoto Y, Yamashita M, Shinohara T, Kanno Y, Jubishi D, Kurano M, Harada S, Okugawa S, Yatomi Y, Moriya K. Dynamic changes in fibrinogen and D-dimer levels in COVID-19 patients on nafamostat mesylate. J Thromb Thrombolysis. 2021 Apr;51(3):649-656.
24. Shimura T, Kurano M, Kanno Y, Ikeda M, Okamoto K, Jubishi D, Harada S, Okugawa S, Moriya K, Yatomi Y. Clot waveform of APTT has abnormal patterns in subjects with COVID-19. Sci Rep. 2021 Mar 4;11(1):5190.
25. Yokoyama R, Kurano M, Morita Y, Shimura T, Nakano Y, Qian C, Xia F, He F, Kishi Y, Okada J, Yoshikawa N, Nagura Y, Okazaki H, Moriya K, Seto Y, Kodama T, Yatomi Y. Validation of a new automated chemiluminescent anti-SARS-CoV-2 IgM and IgG antibody assay system detecting both N and S proteins in Japan. PLoS One. 2021 Mar 4;16(3):e0247711.
26. Nakano Y, Kurano M, Morita Y, Shimura T, Yokoyama R, Qian C, Xia F, He F, Kishi Y, Okada J, Yoshikawa N, Nagura Y, Okazaki H, Moriya K, Seto Y, Kodama T, Yatomi Y. Time course of the sensitivity and specificity of anti-SARS-CoV-2 IgM and IgG antibodies for symptomatic COVID-19 in Japan. Sci Rep. 2021 Feb 2;11(1):2776.
27. Kobayashi T, Nakajima K, Oshima Y, Ikeda M, Kitaura S, Ikeuchi K, Okamoto K, Okada Y, Ohama Y, Higurashi Y, Okugawa S, Moriya K. First Reported Human Case of Spondylodiscitis by Staphylococcus condimenti: A Case Report and Literature Review. Intern Med. 2021 Feb 15; 60(4):635-637.
28. Yamamoto S, Ikeda M, Kanno Y, Okamoto K, Okugawa S, Moriya K. Microbiological analysis of infectious lymphocele: Case series and literature review. J Infect Chemother. 2021 Feb; 27(2):172-178.
29. Harada S, Suzuki M, Sasaki T, Sakurai A, Inaba M, Takuya H, Wakuda M, Doi Y. Transmission of NDM-5-Producing and OXA-48-Producing Escherichia coli Sequence Type 648 by International Visitors without Previous Medical Exposure. Microbiol Spectr. 2021 Dec 22;9(3): e0182721.
30. Nakamura K, Nomoto H, Harada S, Suzuki M, Yomono K, Yokochi R, Hagino N, Nakamoto T, Moriyama Y, Yamamoto K, Kutsuna S, Ohmagari N. Infection with capsular genotype K1-ST23 hypervirulent Klebsiella pneumoniae isolates in Japan after a stay in East Asia: Two cases and a literature review. J Infect Chemother. 2021 Oct;27(10):1508-1512.
31. Takeda K, Harada S, Hayama B, Hoashi K, Enokida T, Sasaki T, Okamoto K, Nakano K, Ohkushi D. Clinical characteristics and risk factors associated with Pneumocystis jirovecii infection in patients with solid tumors: study of thirteen-year medical records of a large cancer center. BMC Cancer. 2021 Sep 3;21(1):987.
32. Harada S, Aoki K, Ohkushi D, Okamoto K, Takehana K, Akatsuchi T, Ida K, Shoji D, Ishii Y, Doi Y, Moriya K, Hayama B. Institutional outbreak involving multiple clades of IMP-producing Enterobacter cloacae complex sequence type 78 at a cancer center in Tokyo, Japan. BMC Infect Dis. 2021 Mar 22;21(1):289.
33. Hosoda T, Harada S, Okamoto K, Ishino S, Kaneko M, Suzuki M, Ito R, Mizoguchi M. COVID-19 and Fatal Sepsis Caused by Hypervirulent Klebsiella pneumoniae, Japan, 2020. Emerg Infect Dis. 2021 Feb;27(2):556-559.
34. Kubota Y, Ishioka H, Harada S, Suzuki M, Shiotsuka J, Lefor AK, Sanui M. Septic shock with emphysematous cholecystitis and

disseminated infection caused by hypervirulent Klebsiella pneumoniae capsular genotype K2-ST65 in a Japanese man with diabetes mellitus: A case report. J Infect Chemother. 2021 Feb;27(2):350-353.

Pathology, Immunology and Microbiology

3. Immunology

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Introduction and Organization

The history of the Department of Immunology, formerly the Department of Serology, dates back to 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, Dr. Tada raised the stature of the department to a world-renowned status. After Dr. Tada's retirement in 1994, Dr. Tadatsugu Taniguchi, presently the project professor of the Department of Molecular Immunology at 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 context of the regulation of immunity and oncogenesis. Dr. Taniguchi's major achievements were the discovery of interferon-β and a new family of transcription factors, termed interferon regulatory factors (IRFs).

On May 2012, Dr. Hiroshi Takayanagi started the new laboratory aiming to shed light on two major questions; First, why self-tolerance are broken in autoimmune diseases? Second, what is the immune network among multiple organs including bone and neuron?

Teaching activities

All members of our department take very seriously their responsibilities to teach and train 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 as Medical Scientist Training Program in faculty of medicine. In fiscal year 2020, special lectures for undergraduate students were given by internationally recognized scientists, Dr. Shimon Sakaguchi (Osaka Univ.), Dr. Hitoshi Sakano (Fukui Univ.), Dr. Hiroshi Kawamoto (Kyoto Univ.), and Dr. Tadatsugu Taniguchi (The Univ. of Tokyo).

Research activities

We aim to achieve 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 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. The crucial stromal cell types that support hematopoietic cell development in the bone marrow have not been clarified. We reported the crucial role of osteoblasts in supporting lymphoid lineage development within the bone marrow micro-environment (Terashima et al., Immunity, 2016). The mice genetically ablated for osteoblasts exhibited a marked reduction of the number of common lymphoid progenitor cells in the bone marrow and mature lymphocytes in the periphery. Our results showed that osteoblasts play a pivotal role in maintenance of common lymphoid progenitors through the production of IL-7. Furthermore, using a mouse model of sepsis, we showed that sepsis rapidly ablated osteoblasts, which reduced the common lymphoid progenitor number and thereby resulted in peripheral lymphopenia. This study demonstrates a reciprocal interaction between the immune and bone systems, in which acute inflammation induces a defect in bone cells resulting in lymphopenia-associated immunodeficiency, suggesting that osteoblasts are a potential therapeutic target of the treatment of inflammatory diseases.

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 TNF family cytokine receptor activator of nuclear factor kappa-B ligand (RANKL). We studied the receptor signal transduction pathway for RANKL and identified nuclear factor of activated T cells c1 (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 (scRNA-seq) analysis on the in vitro osteoclast culture system, and provided a comprehensive picture of molecular processes underlying osteoclastogenesis (Tsukasaki et al., Nat Metab., 2020). We also reported that, using a bone-fracture model in mouse, the cytokine IL-17 promotes bone fracture healing via osteoblastic bone formation and that γδT cells are the major source of IL-17 produced in the bone injury site (Ono et al., Nat Commun., 2016). Although it has been known that IL-17 enhances osteoclastic bone resorption in certain pathological situations, our current results clearly show the promoting effect of IL-17 on bone formation,

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 defense against oral bacteria. This investigation highlighted the notion that T-cell-mediated bone damage, which was considered to be 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 membrane-bound molecule, and cleaved into its soluble form by proteases. We have reported that soluble RANKL is dispensable for 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). These findings provided a new paradigm for physiological interaction between bone and immune system.

2) Lymphocyte development and lymphoid tissue microenvironment

Thymus is the primary lymphoid organ that supports development of useful T cells (positive selection) and eliminates self-reactive T cells (negative selection). The microenvironment of the thymus is mainly composed of thymic epithelial cells that regulate selections of developing T cells.

Recently, we focused on thymic fibroblasts, a stromal cell type with uncharacterized function in the thymus, and established a method to isolate the thymic fibroblast subsets, capsular fibroblasts and medullary fibroblasts. Our results demonstrated that medullary fibroblasts contribute to the induction of T cell self-tolerance by producing a unique set of self-antigens (Nitta et al, Nat Immunol., 2020; Nitta et al, Immunol Rev., 2021). Fibroblasts have been attracting much attention in recent years due to their functional diversity in different organs and their ability to control various biological responses through interactions with immune cells. It is expected that our findings contribute to the elucidation of the functions of various types of fibroblasts in vivo. In addition, we reported that the transcription factor Sox4 is required for the development of thymic tuft cells, a subset of terminally differentiated medullary thymic epithelial cells (mTECs). Our findings suggest that mTECs employ the same transcription programs as peripheral epithelial cells to ‘project’ an immunological self within the thymus for the establishment of central self-tolerance.

We have reported that the genetic variations of human *PSMB11* gene, which encodes β5t, 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). One of the *PSMB11* polymorphisms, G49S, detected in the Japanese population at a high frequency, was associated with a higher risk of Sjögren’s syndrome. These results suggested that, in addition to the MHC haplotype, genetic variations of proteasome influence T cell repertoire selection and susceptibility to autoimmunity. Elucidation of the principles of T-cell repertoire selection is one of most important issues in immunology. We have been continuing our research efforts including a recent release of updated protocols for gene transduction method optimized for T-cell repertoire analysis (Muro et al, Methods Mol Biol., 2020).

We have also been studying on thymic development of γδT cells. We showed that the γδTCR signal mediated by the Syk-PI3K pathway is essential for thymic development of IL-17-producing γδT cells (Muro et al., J Clin Invest., 2018). These findings suggest that the Syk-PI3K pathway might be a

therapeutic target of inflammatory diseases. Recently, we generated mutant mice lacing all of the Skint family genes (Skint1-11) that encode candidate thymic factors for regulation of γδT cell development (Narita et al., Int Immunol., 2018). These mice exhibited a marked reduction of Vγ5Vδ1 γδT cells in the thymus and skin, but had normal development of other γδT cell subsets and leukocytes. This study indicates an exclusive function of Skint family genes in the development of Vγ5Vδ1 γδT cells and provides a useful animal model to analyze the mechanism for thymic education of γδT cells.

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 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 microfold (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 (MCi) cells) are key players in the maintenance of host-microbe symbiosis. Furthermore, we reported that Col6a1-Cre driver mice are useful to study 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 (γc) 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 γc and JAK3. In recent years, Jak inhibitors have attracted attention as potential agents for the autoimmune diseases such as rheumatoid arthritis. This study presented an entirely new regulatory mechanism governing γc 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 IκBζ as an indispensable transcription factor for Th17 cell differentiation (Okamoto et al., Nature, 2010). However, in both RA and EAE models, 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). 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 show that the targeting these cells and/or molecules could be effective in preventing bone destruction in RA.

To elucidate a role of RANKL on T cells, we generated T cell-specific RANKL-deficient mice. These mice were protected from EAE, a mouse model of multiple sclerosis, due to an impairment of infiltration of pathogenic T cells into the central nervous system (CNS). RANKL on T cells stimulates the chemokine production by astrocytes, leading to the chronic inflammation in the CNS. Pharmacological inhibition of RANKL prevented the development of

EAE, indicating that RANKL is a potential therapeutic target for treatment of multiple sclerosis (Guerrini et al., Immunity, 2015).

We have also been studying the mechanism of T cell 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 mTECs ectopically express a variety of tissue-restricted antigens (TRAs) and thereby TRA-reactive immature T cells are deleted. It has been known that 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 Chd4 as chromatin remodeler interacting with Fezf2. Chd4 works with not only Fezf2 but Aire to promote promiscuous TRA expression in mTECs, mediating central immune tolerance (Tomofuji et al., Nat Immunol., 2020). Thus, these studies represented important advance in our understanding of the mechanisms underlying the immune tolerance and autoimmune diseases.

References

1. Tsukasaki M, Takayanagi H. Osteoimmunology: evolving concepts in bone-immune interactions in health and disease. ***Nat Rev Immunol.***, 19: 626-642 (2019)
2. Tsukasaki et al., Stepwise cell fate decision pathways during osteoclastogenesis at single-cell resolution. ***Nat Metab.***, 2: 1382–1390 (2020)
3. Tsukasaki et al., OPG Production Matters Where It Happened. ***Cell Rep.***, 2: 1382–1390 (2020)
4. Nitta et al., Fibroblasts as a source of self-antigens for central immune tolerance. ***Nat Immunol.***, 21: 1172–1180 (2020)
5. Nitta et al., The fibroblast: an emerging key player in thymic T cell selection. ***Immunol Rev***, 302: 68-85 (2021)
6. Muro R, Takayanagi H, Nitta T. Retroviral gene transduction into T-cell progenitors for analysis of T cell development in the thymus. ***Methods Mol Biol.***, 2111, 193-203 (2020)
7. Mino et al., The Transcription Factor Sox4 is Required for Thymic Tuft Cell Development. ***Int Immunol.***, 34: 45-52 (2022)
8. Komatsu et al., Plasma cells promote osteoclastogenesis and periarticular bone loss in autoimmune arthritis. ***J Clin Invest.***, 131: e143060 (2021)
9. Tomofuji et al., Chd4 choreographs self-antigen expression for central immune tolerance. ***Nat Immunol.***, 21: 892–901 (2020)

Radiology and Biomedical Engineering

1. Radiology

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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 1 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 centralized Clinical Radiology Service Department 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 new inpatient building, 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-dimensional (3D) fashion. Using the data acquired by MDCT, various kinds of diseases in almost all parts of the body, from cerebral diseases to musculoskeletal diseases, can be displayed in 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 a new staff from the Faculty of Engineering, the University of Tokyo. 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, MR digital subtraction angiography, perfusion imaging, and diffusion imaging are the foci of research. 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 (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 cerebro-vascular 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.

Publications

One hundred and thirty seven, 83, and 98 English original articles have been published from our department in 2021, 2020, and 2019. respectively. Please refer to our homepage, http://www.ut-radiology.umin.jp/publication/2021.html.

Radiology and Biomedical Engineering

2. Biomedical Engineering

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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 adrenomedulin 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 re-modeling, 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-deficent 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 mechano-transduction 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 (MβCD), a membrane-cholesterol-depleting agent, increased mitochondrial ATP production. The addition of cholesterol to cells inhibited the increasing effects of both shear stress and MβCD 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

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References

1. H. Tani, B. Li, T. Kusu, R. Okumura, J. Nishimura, D. Okuzaki, D. Motooka, S. Nakamura, S-H. Tsai, Y. Furuta, M. Muneta, K. Yamamoto, H. Yagita, H. Kayama, and K. Takeda. The ATP-hydrolyzing ectoenzyme E-NTPD8 attenuates colitis through modulation of P2X4 receptor-dependent metabolism in myeloid cells**.** ***Proc. Natl. Acad. Sci. USA.*** 118 (39): e2100594118, 2021.
2. T. Hirata, K. Yamamoto, K. Ikeda, and M. Arita. Functional lipidomics of vascular endothelial cells in response to laminar shear stress. ***FASEB J.*** 35: 1-13 (e21301), 2021.

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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 1 postdoctoral researcher, 8 PhD students, one master course students, one technical staff, as of FY2020.

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

Our lab aims at developing novel fluorescence probes and applying these molecules to biology and medicine. So far, we have succeeded in establishing rational design strategies of fluorescence probes based on several mechanisms including intramolecular spirocyclization. In FY2020, we have developed a coumarin-hemicyanine hybrid fluorescent probe for hydrases, a fluorescent probe for super-resolution microscopy that blinks by the reaction with intracellular glutathione, a γ-glutamyltranspeptidase (GGT)-detecting fluorescence probe with high cellular retention, fluorescence probes for glycosidases to detect breast cancers, and Activatable Raman Probes for Simultaneous Detection of Plural Enzyme Activities. The details are described below.

Coumarin-hemicyanine fluorophores (CHCs) have unique properties such as fluorescence in the red region, large Stokes shift, and compatibility with ratiometric measurement. By incorporating intramolecular spirocyclization as a switching mechanism, we have succeeded in developing a new fluorescent probe that reacts with GGT and esterases to significantly change their fluorescence properties. (Reference [1])

Single-molecule localization microscopy (SMLM) is a powerful technique for super-resolution imaging, but its implementation has generally been limited by the need for intense laser irradiation and additives to force molecular blinking. We have succeeded in developing new fluorescent probes that spontaneously blink in response to intracellular glutathione, and used them to perform super-resolution imaging of microtubules and mitochondria in living cells. (Reference [2])

Hydroxymethyl rhodamine (HMR) derivatives are fluorophores that enable the development of various fluorogenic and super-resolution fluorescent imaging

probes by appropriately controlling the intramolecular spirocyclization equilibrium (equilibrium between open and closed forms) and the lifetime of the open form. On the other hand, the development of fluorescent probes with optimized properties required a time-consuming and labor-intensive process of synthesizing various derivatives to identify fluorescent probes bearing the desired properties. We have developed a quantum chemical calculation method to accurately predict the properties of these fluorescent probes in silico, enabling us to develop fluorescent probes with desired properties with high probability by rational design without synthesizing a large number of derivatives. In addition, this has enabled us to develop multicolor cancer imaging fluorescent probes and super-resolution fluorescent imaging probes (Ref. [3, 4]).

Although fluorescent probes that detect GGT activity are extremely useful for cancer visualization, conventional probes have the disadvantage of leaking from the cells after prolonged imaging and fixation processes. We have succeeded in developing a probe that reacts with GGT followed by nucleophilic attack by intracellular nucleophiles including proteins and glutathione, enabling the fluorescent product to be trapped inside the cells. By using a patient-derived xenograft model, we have shown that this probe is indeed resistant to fixation and immunostaining. (Reference [5])

Fluorescent probes to detect breast cancer are extremely useful tools for fluorescence-guided surgery of breast cancer, but conventional probes have shown considerable background fluorescence even in normal tissues. We focused on glycosidase activity, which is highly expressed in breast cancer, and developed a library of fluorescent probes containing various sugars. As a result, we found that the fluorescent probe with α-mannose showed good results and that the target enzyme was α-mannosidase 2C1. We also found that simultaneous multicolor imaging with a probe targeting GGT can distinguish between malignant and benign tumors. (Reference [6])

Alkyne- and nitrile-tagged Raman probes are extremely useful for multiplex imaging, but it has been difficult to develop activatable Raman probes that visualize enzyme activity. By applying our accumulated knowledge of the properties of xanthene dyes, we have succeeded in developing a general strategy to prepare activatable Raman probes that show enhanced Raman signals due to electronic preresonance (EPR) upon reaction with enzymes under physiological conditions. By using the probes, we succeeded in visualizing multiple enzyme activities simultaneously in living cells. (Reference [7], collaborative research with Ozeki Laboratory, Graduate School of Engineering, the University of Tokyo).

We also performed several collaborative works (Reference 8-12).

References

[1] H. Fujioka, S.N. Uno, M. Kamiya, R. Kojima, K. Johnsson, Y. Urano, Activatable fluorescent probes for hydrolase enzymes based on coumarin-hemicyanine hybrid fluorophores with large Stokes shifts, *Chem. Commun.* 56 (2020) 5617-5620.

[2] A. Morozumi, M. Kamiya, S.N. Uno, K. Umezawa, R. Kojima, T. Yoshihara, S. Tobita, Y. Urano, Spontaneously Blinking Fluorophores Based on Nucleophilic Addition/Dissociation of Intracellular Glutathione for Live-Cell Super-resolution Imaging, *J. Am. Chem. Soc.* 142 (2020) 9625-9633.

[3] R. Tachibana, M. Kamiya, A. Morozumi, Y. Miyazaki, H. Fujioka, A. Nanjo, R. Kojima, T. Komatsu, T. Ueno, K. Hanaoka, T. Yoshihara, S. Tobita, Y. Urano, Design of spontaneously blinking fluorophores for live-cell super-resolution imaging based on quantum-chemical calculations, *Chem. Commun.* 56 (2020) 13173-13176.

[4] R. Tachibana, M. Kamiya, S. Suzuki, K. Morokuma, A. Nanjo, Y. Urano, Molecular design strategy of fluorogenic probes based on quantum chemical prediction of intramolecular spirocyclization, *Commun. Chem.* 3 (2020) 82.

[5] R. Obara, M. Kamiya, Y. Tanaka, A. Abe, R. Kojima, T. Kawaguchi, M. Sugawara, A. Takahashi, T. Noda, Y. Urano, gamma-Glutamyltranspeptidase (GGT)-Activatable Fluorescence Probe for Durable Tumor Imaging, *Angew. Chem. Int. Ed.* 60 (2021) 2125-2129.

[6] K. Fujita, M. Kamiya, T. Yoshioka, A. Ogasawara, R. Hino, R. Kojima, H. Ueo, Y. Urano, Rapid and Accurate Visualization of Breast Tumors with a Fluorescent Probe Targeting alpha-Mannosidase 2C1, *ACS Cent. Sci.* 6 (2020) 2217-2227.

[7] H. Fujioka, J. Shou, R. Kojima, Y. Urano, Y. Ozeki, M. Kamiya, Multicolor Activatable Raman Probes for Simultaneous Detection of Plural Enzyme Activities, *J. Am. Chem. Soc.* 142 (2020) 20701-20707.

[8] T. Akashi, H. Isomoto, K. Matsushima, M. Kamiya, T. Kanda, M. Nakano, T. Onoyama, M. Fujii, J. Akada, Y. Akazawa, K. Ohnita, F. Takeshima, K. Nakao, Y. Urano, A novel method for rapid detection of a Helicobacter pylori infection using a gamma-glutamyltranspeptidase-activatable fluorescent probe, *Sci. Rep.* 9 (2019) 9467.

[9] T. Asano, Y. Nagayo, S. Tsuda, A. Ito, W. Kobayashi, K. Fujita, K. Sato, K.M. Nishiguchi, H. Kunikata, H. Fujioka, M. Kamiya, Y. Urano, T. Nakazawa, Companion Diagnosis for Retinal Neuroprotective Treatment by Real-Time Imaging of Calpain Activation Using a Novel Fluorescent Probe, *Bioconjugate Chem.* 31 (2020) 2241-2251.

[10] S. Kawashima, T. Yoshioka, H. Hino, K. Kitano, K. Nagayama, M. Sato, R. Kojima, M. Kamiya, Y. Urano, J. Nakajima, & x264; -glutamyl hydroxymethyl rhodamine green fluorescence as a prognostic indicator for lung cancer, *Gen. Thorac. Cardiovas.* 68 (2020) 1418-1424.

[11] Y. Kono, T. Ishizawa, N. Kokudo, Y. Kuriki, R.J. Iwatate, M. Kamiya, Y. Urano, A. Kumagai, H. Kurokawa, A. Miyawaki, K. Hasegawa, On-Site Monitoring of Postoperative Bile Leakage Using Bilirubin-Inducible Fluorescent Protein, *World J. Surg.* 44 (2020) 4245-4253.

[12] K. Yamamoto, S. Ohnishi, T. Mizushima, J. Kodaira, M. Ono, Y. Hatanaka, K.C. Hatanaka, Y. Kuriki, M. Kamiya, N. Ehira, K. Shinada, H. Takahashi, Y. Shimizu, Y. Urano, N. Sakamoto, Detection of early adenocarcinoma of the esophagogastric junction by spraying an enzyme-activatable fluorescent probe targeting Dipeptidyl peptidase-IV, *BMC Cancer*, 20 (2020) 64.

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Lecturer

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Introduction and Organization

As the first research institute for medical engineering in Japan, Institute of Medical Electronics was established in 1963. Department of Clinical Medicine in the Institute of Medical Electronics was started in 1964 for research and development of advanced diagnostic and therapeutic medical engineering technologies. To date, medical engineering has grown up not only to a very important academic discipline but also to a very important means for clinical medicine. With the structural reformation of Faculty of Medicine, Institute of Medical Electronics has been shifted to Graduate School of Medicine, and Department of Clinical Medicine in the Institute of Medical Electronics has been reformed to the present department since April 1, 1997.

The current members include a lecturer, one graduate student, a senior technical specialist, and a project academic support staff.

Since our research covers wide area of inter-disciplinary and comprehensive research fields based on the advanced medical and engineering technologies, we are cooperating with various laboratories.

Teaching activities

We take a part in systematic lectures for the 3rd year medical students. We also provide practice in the “free quarter” course for the 2nd year medical students. In systematic lectures, we teach an introduction of the advanced diagnostic and therapeutic medical engineering technologies. The lectures for artificial organ technologies are included.

For post-graduate education, we provide lectures for the master course students, and we take a part in series of lectures for the doctor course students. For the master course students, we offer lectures on artificial organ technologies. For the doctor course students, we offer lectures on advanced medical engineering technologies.

The educational practice of the post-graduate students is performed mainly by on-the-job training method in the daily research works. Through the development and animal experiments of the artificial hearts, research strategy, methods of in-vitro, ex-vivo and in-vivo studies, design and fabrication techniques, machining technique, pre-operative management, anesthesia, surgery, post-operative management, measurement, data processing, ethical factor, and other important knowledge, techniques and experiences are acquired. In the practice, we give the master course students several assignments from the field of the artificial organs as a subject of their research. The doctor course students have to find the subject of their research by themselves. The research subject of the doctor course students is not limited to the field of the artificial organs but is found from the wide area of advanced medical and engineering technologies.

Students must attend research and development meeting. They can learn how to perform the research work and how to report it through the meeting.

The education to train the leaders of medical engineers and clinical engineers is another important role of our laboratory.

Research activities

Our research field covers advanced diagnostic and therapeutic medical engineering technologies for clinical medicine. The main subjects are artificial organs (artificial hearts, assist circulations, artificial lungs, artificial valves, tissue engineered artificial organs, regenerative artificial organs, etc.). Especially, the artificial heart is our world famous research project having a long history since 1959. Concerning the artificial heart, almost all the researches and developments for driving mechanisms, energy converters, blood pumps, biomaterials, power transmissions, measurement techniques, control methods, anatomical fitting, blood compatibility, tissue compatibility, computational fluid dynamics (CFD) analysis, physiology, pathology, and so on, have been studied. All the stuffs and students are in part participating in the artificial heart project. In 1995, we succeeded to survive a goat for 532 days with the paracorporeal total artificial heart (TAH) with no anticoagulant, which is still the longest surviving record of TAH animals in the world.

Our artificial heart research at present is to develop a totally implantable TAH with high performance, good anatomical fitting, high durability, high reliability, high efficiency, good controllability, and excellent biological compatibility, which can be implanted in the body of small stature like Japanese. To meet the purpose, we had been developing the TAH using undulation pumps, named undulation pump TAH (UPTAH). The undulation pump is our original blood pump invented in 1992. The UPTAH revealed to have an excellent performance and the goat whose heart was replaced with the UPTAH survived for 153 days. However, the UPTAH had a problem in the durability of the complex drive shaft mechanism. To improve the problem of the UPTAH, a new blood pump, named the helical flow pump (HFP), was invented in our laboratory in 2005. The HFP is a novel blood pump having a hydrodynamic levitating impeller, which promises high durability. The animal experiment of the helical flow TAH (HFTAH) had started in 2011. The HFTAH could be implanted in the goat successfully with good anatomical fitting. To date, the goat whose heart was replaced with the HFTAH survived for 100 days. We are expecting to develop an ideal TAH that surpass the outcome of the heart transplantation with combination of the technologies of the physiological control and hybrid materials described later.

How to control the output of a TAH is primary interest. We have developed our original physiological control method of the TAH, named 1/R control. The 1/R control was developed with a conductance (1/R: reciprocal of a resistance) parallel circuit model. With the 1/R control, the particular problems of a TAH such as venous hypertension, slight anemia, low thyroid hormone level and so on, were not observed and the output changed in accordance with a metabolic demand of the animal.

The problem of the 1/R control was a mismatching of the time constants between the control systems of the device and the body. As a consequence, the 1/R control occasionally diverged in the animal experiment of the UPTAH and HFTAH. To improve the problem of instability in the 1/R control, a new control method based on the fluctuation of arterial and venous pressures (named ΔP control) was developed by reforming the 1/R control function. At present, ΔP control is tested with the animal experiment.

On the other hand, the 1/R control was applied to the UPTAH and HFTAH to perform a physiological study with a nonpulsatile TAH by changing the drive mode from pulsatile to nonpulsatile in a single goat. The result showed that, for a period of several weeks, the 1/R control could be promising not only with a pulsatile flow, but also with a nonpulsatile flow. The general conditions and organ functions were not changed by the application of the nonpulsatile flow. The cardiac output and the arterial pressure changed with the condition of the goat in the pulsatile and also nonpulsatile flow, which seemed almost identical. However, under the physiological atrial pressure, the sucking effect of atria was more significant in the nonpulsatile flow than the pulsatile flow. Therefore, the nonpulsatile TAH with the 1/R control was considered to be inadequate, unless some pulsatility would be introduced to avoid the sucking effect for ensuring sufficient inflow condition.

Concerning the materials, we have been developing a new method to develop hybrid materials. In general, it is not easy to develop mechanical parts for complex artificial organs such as artificial hearts from the

components of living tissue because these components have insufficient strength and durability, even though they have excellent tissue compatibility. To overcome these problems, an insert molding method, which is commonly used for resin molding in the industrial field, was introduced. In this method, the mold, in which an artificial material was inserted, was implanted in the animal, and the tissue grew into the mold to make a hybrid material. The method was first applied to the Jellyfish valve that was originally a polymer valve for the artificial hearts. The hybrid Jellyfish valve demonstrated a good result. Then, we started to develop the hybrid conduit of the inflow cannula for the left ventricular assist device (LVAD). The conduit is inserted into the apex of the left ventricle where the thrombus often formed. In this method, the mold in which the core of the conduit was inserted was implanted under the skin of a goat. After several months, the hybrid conduit was extirpated, and then freeze-dried, sterilized and used. The experiment of the LVAD using the hybrid conduit is going on with a goat. This hybrid technique will be an important technology for developing the next generation artificial organs.

A project of the novel gas-exchange system for bridging to lung transplantation has been performed in an AMED project. The device consists of a blood pump, an oxygenator, a drive and control unit, and a battery unit. To realize several-months support, the left side blood pump of helical flow TAH has been employed. This system is expected to offer more opportunities and safer surgical interventions to those who are waiting for lung transplants. In case of high afterload, the sequential flow pump (SFP) would be applied. The SFP in which fluid is given centrifugal force sequentially twice in a pump was invented in our laboratory in 2013. This sequential pressurization mechanism enables high-pressure output without high impeller speed, which can reduce the sheer stress of the blood. To realize integration of the pump with the artificial lung, inlet and outlet ports are located at lateral side and center of the pump, respectively, which is the reverse configuration of conventional centrifugal pumps.

References

1. Yusuke INOUE, Ayaka TASHIRO, Yukino KAWASE, Takashi ISOYAMA, Itsuro SAITO, Toshiya ONO, Shintaro HARA, Kohei ISHII, Terumi YURIMOTO, Yasuyuki SHIRAISHI, Akihiro YAMADA, Tomoyuki YAMBE, Yusuke ABE, Optimum Sterilization Methods of Biocompatible Hybrid Material for Artificial Organs. Advanced Biomedical Engineering 9: 2020 83-92,2020

Division of Integrative Genomics

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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

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. Iwasaki A, Shinozaki-Ushiku A, Kunita A, Yamazawa S, Sato Y, Yamashita H, Fukayama M, Seto Y, Ushiku T: Human Leukocyte Antigen Class I Deficiency in Gastric Carcinoma: An Adaptive Immune Evasion Strategy Most Common in Microsatellite Instable Tumors. ***Am J Surg Pathol*** 45:1213-1220,2021.
2. Nagano M, Kohsaka S, Hayashi T, Ueno T, Kojima S, Shinozaki-Ushiku A, Morita S, Tsuda M, Tanaka S, Shinohara T, Omori Y, Sugaya F, Kato H, Narita Y, Nakajima J, Suzuki K, Takamochi K, Mano H: Comprehensive molecular profiling of pulmonary pleomorphic carcinoma. ***NPJ Precis Oncol*** 5:57,2021.
3. Sasaki K, Honda A, Shinozaki-Ushiku A, Fujioka Y, Maki H, Toyama K, Ushiku T, Kurokawa M: A case of transplantation-associated thrombotic microangiopathy with autopsy-proven fatal myocardial ischemia after allogeneic hematopoietic stem cell transplantation. ***Ann Hematol*** 100:1621-1622,2021.
4. Sato A, Tanabe M, Tsuboi Y, Niwa T, Shinozaki-Ushiku A, Seto Y, Murakami Y: Circulating Tumor DNA Harboring the BRAF(V600E) Mutation May Predict Poor Outcomes of Primary Papillary Thyroid Cancer Patients. ***Thyroid*** 31:1822-1828,2021.
5. Yoshioka K, Kurokawa R, Amemiya S, Koyamaa H, Matsuda K, Honda A, Kurokawa M, Shinozaki-Ushiku A, Abe O: Rapidly progressing blastic plasmacytoid dendritic cell neoplasm causing diffuse skin thickening: A case report with sequential computed tomography examinations. ***Radiol Case Rep*** 16:2929-2933,2021.
6. Tsuzuki S, Komai T, Terada K, Tsuchida Y, Tanaka M, Tateishi Y, Shinozaki-Ushiku A, Shoda H, Fujio K: Nailfold capillaroscopic abnormalities in angioedema with eosinophilia. ***Allergol Int*** 70:501-503,2021.
7. Tanaka R, Kaburaki T, Taoka K, Karakawa A, Tsuji H, Nishikawa M, Yatomi Y, Shinozaki-Ushiku A, Ushiku T, Araki F: More Accurate Diagnosis of Vitreoretinal Lymphoma Using a Combination of Diagnostic Test Results: A Prospective Observational Study. ***Ocul Immunol Inflamm*** Apr 1; 1-7,2021.
8. Kato S, Kubota Y, Sekiguchi M, Watanabe K, Shinozaki-Ushiku A, Takita J, Hiwatari M: KMT2A-rearranged diffuse large B-cell lymphoma in a child: a case report and molecular characterization. ***Pediatr Hematol Oncol*** 38:281-289,2021.
9. Kobayashi H, Makise N, Shinozaki-Ushiku A, Ishibashi Y, Ikegami M, Kohsaka S, Ushiku T, Oda K, Miyagawa K, Aburatani H, Mano H, Tanaka S: Scapular Angiomatoid Fibrous Histiocytoma with EWSR1-CREB1 Fusion in an Adult Patient. ***Case Rep Orthop***:9434222,2021.
10. Ikeda Y, Adachi K, Tomio K, Eguchi-Kojima S, Tsuruga T, Uchino-Mori M, Taguchi A, Komatsu A, Nagamatsu T, Oda K, Kawana-Tachikawa A, Uemura Y, Igimi S, Osuga Y, Fujii T, Kawana K: A Placebo-Controlled, Double-Blind Randomized (Phase IIB) Trial of Oral Administration with HPV16 E7-Expressing Lactobacillus, GLBL101c, for the Treatment of Cervical Intraepithelial Neoplasia Grade 2 (CIN2). ***Vaccines (Basel)*** 9:329,2021.
11. Yamaguchi K, Matsumoto Y, Suzuki R, Nishida H, Omata D, Inaba H, Kukita A, Tanikawa M, Sone K, Oda K, Osuga Y, Maruyama K, Fujii T: Enhanced antitumor activity of combined lipid bubble ultrasound and anticancer drugs in

gynecological cervical cancers. ***Cancer Sci*** 112: 2493-2503,2021.

12. Takahashi Y, Sone K, Noda K, Yoshida K, Toyohara Y, Kato K, Inoue F, Kukita A, Taguchi A, Nishida H, Miyamoto Y, Tanikawa M, Tsuruga T, Iriyama T, Nagasaka K, Matsumoto Y, Hirota Y, Hiraike-Wada O, Oda K, Maruyama M, Osuga Y, Fujii T: Automated system for diagnosing endometrial cancer by adopting deep-learning technology in hysteroscopy. ***PLoS One*** 16:e0248526,2021.
13. Kawata A, Taguchi A, Baba S, Miyamoto Y, Tanikawa M, Sone K, Tsuruga T, Mori M, Oda K, Kawana K, Osuga Y, Fujii T: A low preoperative albumin-to-globulin ratio is a negative prognostic factor in patients with surgically treated cervical cancer. ***Int J Clin Oncol*** 26:980-985,2021.
14. Halimi SA, Maeda D, Ushiku-Shinozaki A, Goto A, Oda K, Osuga Y, Fujii T, Ushiku T, Fukayama M: Comprehensive immunohistochemical analysis of the gastrointestinal and Mullerian phenotypes of 139 ovarian mucinous cystadenomas. ***Hum Pathol*** 109:21-30,2021.
15. Naito Y, Aburatani H, Amano T, Baba E, Furukawa T, Hayashida T, Hiyama E, Ikeda S, Kanai M, Kato M, Kinoshita I, Kiyota N, Kohno T, Kohsaka S, Komine K, Matsumura I, Miura Y, Nakamura Y, Natsume A, Nishio K, Oda K, Oda N, Okita N, Oseto K, Sunami K, Takahashi H, Takeda M, Tashiro S, Toyooka S, Ueno H, Yachida S, Yoshino T, Tsuchihara K: Clinical practice guidance for next-generation sequencing in cancer diagnosis and treatment (edition 2.1). ***Int J Clin Oncol*** 26:233-283,2021.
16. Matsuo K, Matsuzaki S, Nusbaum DJ, Maoz A, Oda K, Klar M, Roman LD, Sood AK: Possible candidate population for neoadjuvant chemo-therapy in women with advanced ovarian cancer. ***Gynecol Oncol*** 160:32-39,2021.

Neuroscience

1. Basic Neuroscience

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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 (Aβ) ending at 40th or 42nd residues (Aβ40 and Aβ42, 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 Aβ42, 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 celllar 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 Aβ42 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 Aβ, 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 APH-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,

APH-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 cystein 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 immuno-histochemical analysis of Aβ 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-Aβ Alzheimer amyloid plaque component CLAC, and its precursor CLAC-P

The major component of Alzheimer's amyloid plaques is Aβ, although there are a number of non-Aβ 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 Aβ 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 Aβ in vitro. Knockout mice studies have confirmed the role of CLAC in neuromuscular development (Tanaka et al. J Neurosci, 2014).

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: clinical studies for the identification of surrogate imaging and biomarkers of 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).

References

1) Matsukawa K, Kukharsky, Park S-K, Park S, Iwatsubo T, Hashimoto T, Liebman S, Shelkovnikova T: Long non-coding RNA NEAT1 ameliorates TDP-43 toxicity in *in vivo* models of TDP-43 proteinopathy. ***RNA Biol*** 1-9, 2021
2) Sato K, Ihara R, Suzuki K, Niimi Y, Toda T, Jimenez-Maggiora G, Langford O, Donohue MC, Raman R, Aisen PS, Sperling RA, Iwata A, Iwatsubo T: Predicting amyloid risk by machine learning algorithms based on the A4 screen data: application to the Japanese Trial-Ready Cohort study. ***Alzheimers Dementia: Translational Research & Clinical Interventions*** 7:e12135, 2021
3) Levine SZ, Goldberg Y, Yoshida K, Samara M, Cipriani A, Iwatsubo T, Leucht S, Furuwaka TA: Quantifying the heterogeneity of cognitive functioning in Alzheimer's disease to extend the placebo-treatment dichotomy: latent class analysis of individual-participant data from Five pivotal randomized clinical trials of donepezil. ***European Psychiatr*** 64: e16, 2021
4) Levine SZ, Yoshida K, Goldberg Y, Samara M, Cipriani A, Efthimiou O, Iwatsubo T, Leucht S, Furukawa TA: Linking the Mini-Mental State Examination, the Alzheimer's Disease Assessment Scale-Cognitive Subscale and the Severe Impairment Battery: Evidence from five randomized clinical trials. ***Evid Based Ment Health*** 24:56-61, 2021
5) Sato K, Niimi Y, Ihara R, Suzuki K, Toda T, Iwata A, Iwatsubo T: Efficacy and cost-effectiveness of multiple promotion methods to recruit participants to online screening registry for the facilitation of Alzheimer's disease prevention trials. ***J Med Internet Res*** 23:e26284, 2021
6) Mano T, Sato K, Ikeuchi T, Toda T, Iwatsubo T, Iwata A: Peripheral blood BRCA1 methylation positively correlates with major Alzheimer's disease risk factors. ***J Prev Alzheimers Dis*** 8:477-482, 2021
7) Ochiai T, Nagayama T, Matsui K, Amano K, Sano T, Wakabayashi T, Iwatsubo T: Tauroursodeoxycholic acid attenuates diet-induced and age-related peripheral endoplasmic reticulum stress and cerebral amyloid pathology in a mouse model of Alzheimer's disease. ***J Prev Alzheimers Dis*** 4:483-494, 2021
8) Senda M, Ishii K, Ito K, Ikeuchi T, Matsuda H, Iwatsubo T, Iwata A, Ihara R, Suzuki K, Kasuga K, Ikari Y, Niimi Y, Arai H, Tamaoka A, Arahata Y, Itoh Y, Tachibana H, Ichimiya Y, Washizuka S, Odawara T, Ishii K, Ono K, Yokota T, Nakanishi A, Matsubara E, Mori H, Shimada H: A Japanese multicenter study on PET and other biomarkers for subjects with potential preclinical and pro-

dromal Alzheimer's disease. ***J Prev Alzheimers Dis*** 8:495-502, 2021

9) Sato K, Mano T, Ihara R, Suzuki K, Toda T, Iwatsubo T, Iwata A: Cohort-specific optimization of models predicting preclinical Alzheimer's disease, to enhance screening performance in the middle of preclinical Alzheimer's disease clinical studies. ***J Prev Alzheimers Dis*** 8:503-512, 2021
10) Sato K, Mano T, Niimi Y, Toda T, Iwata A, Iwatsubo T: Facial nerve palsy following the administration of mRNA COVID-19 vaccines. ***Int J Infect Dis*** 111:310-312, 2021
11) Ochiai T, Sano T, Kubota N, Kadowaki T, Wakabayashi T, Iwatsubo T: Differential involvement of insulin receptor substrate (IRS)-1 and IRS-2 in brain insulin signaling is associated with the effects of their deficiency on amyloid pathology in Alzheimer's disease. ***Neurobiol Dis*** 159:105510, 2021
12) Samara MT, Levine SZ, Yoshida K, Goldberg Y, Clipriani A, Efthimiou O, Iwatsubo T, Leucht S, Furukawa TA: Linking the clinical dementia rating scale-sum of boxes, the clinician's interview-based impression plus caregiver input and the clinical global impression scale: Evidence based on individual participant data from five randomized clinical trials of donepezil. ***J Alz Dis*** 82:1075-1084, 2021
13) Sato K, Mano T, Niimi Y, Iwata A, Toda T, Iwatsubo T: The impact of COVID-19 pandemic on the provision of ambulatory care for patients with chronic neurological diseases in Japan: evaluation of an administrative claims database. ***BioScience Trends*** 15:219-230, 2021
14) Koh HS, Lee SJ, Lee HJ, Min J-W, Iwatsubo T, Teunissen CE, Cho H-J, Ryu J-H: Targeting microRNA-485-3p blocks Alzheimer's disease progression. ***Int J Mol Sci*** 22:13136, 2021
15) Komaki K, Takano T, Sato Y, Asada A, Ikeda S, Yamada K, Wei R, Huo A, Saito T, Ando K, Murayama S, Araki W, Kametani F, Hasegawa M, Iwatsubo T, Tomomura M, Fukuda M, Hisanaga S-I: Lemur tail kinase 1 (LMTK1) regulates the endosomal localization of b-secretase BACE1. ***J Biochem*** 170:729–738, 2021

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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 Univiersity) 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, two postdoctoral scholars, one technical staff, eight Ph.D. graduate students, one technical assistant and three 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 modifications 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/CaMKIγ) 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/CaMKIγ 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 re-generative 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 CaMKIIα and calcineurin are fine-tuned to unique bandwidths and compute input variables in an asymmetric manner (Fujii et al., Cell Reports 2013).

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).

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-1α 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-1α 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 mDia1 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 2021- December 2021)

1. Ueda S, Hosokawa M, Arikawa K, Takahashi K, Fujiwara M, Kakita M, Fukada T, Koyama H, Horigane SI, Itoi K, Kakeyama M, Matsunaga H, Takeyama H, Bito H, Takemoto-Kimura S. Distinctive Regulation of Emotional Behaviors and Fear-Related Gene Expression Responses in Two Extended Amygdala Subnuclei With Similar Molecular Profiles. Front Mol Neurosci. 2021 Sep 3, 14:741895. Doi: 10.3389/fnmol.2021. 741895.

2. Ohnishi T, Kiyama Y, Arima-Yoshida F, Kadota M, Ichikawa T, Yamada K, Watanabe A, Ohba H, Tanaka K, Nakaya A, Horiuchi Y, Iwayama Y, Toyoshima M, Ogawa I, Shimamoto-Mitsuyama C, Maekawa M, Balan S, Arai M, Miyashita M, Toriumi K, Nozaki Y, Kurokawa R, Suzuki K, Yoshikawa A, Toyota T, Hosoya T, Okuno H, Bito H, Itokawa M, Kuraku S, Manabe T, Yoshikawa T. Cooperation of LIM domain-binding 2 (LDB2) with EGR in the pathogenesis of schizophrenia. EMBO Mol Med. 2021 Apr 9, 13(4):e12574. Doi: 10.15252/emmm.202012574.
3. Sulistomo HW, Nemoto T, Kage Y, Fujii H, Uchida T, Takamiya K, Sumimoto H, Kataoka H, Bito H, Takeya R. Fhod3 Controls the Dendritic Spine Morphology of Specific Subpopulations of Pyramidal Neurons in the Mouse Cerebral Cortex. Cereb Cortex. 2021 Mar 5, 31(4):2205-2219. Doi: 10.1093/cercor/bhaa355.
4. Horigane SI, Hamada S, Kamijo S, Yamada H, Yamasaki M, Watanabe M, Bito H, Ohtsuka T, Takemoto-Kimura S. Development of an L-type Ca2+ channel-dependent Ca2+ transient during the radial migration of cortical excitatory neurons. Neurosci Res. 2021 Aug, 169:17-26. Doi: 10.1016/j.neures.2020.06.003.
5. Benner S, Aoki Y, Watanabe T, Endo N, Abe O, Kuroda M, Kuwabara H, Kawakubo Y, Takao H, Kunimatsu A, Kasai K, Bito H, Kakeyama M, Yamasue H. Neurochemical evidence for differential effects of acute and repeated oxytocin administration. Mol Psychiatry. 2021 Feb, 26(2): 710-720. doi: 10.1038/s41380-018-0249-4.

Neuroscience

2. Integrative Medical Neuroscience

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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 2021, we had 6 graduate students (1 in master course and 6 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 2021 are as follows:

- Epidemiological, behavior phenotype, neuropsychological, and treatment study of Tourette syndrome and child & adolescent OCD
- Brain-imaging study of ASD, ADHD and Tourette syndrome by structural-MRI, functional-MRI and near-infrared spectroscopy (NIRS)
- Development of predictor of parent training for ADHD
- Effectiveness study of early intervention for autistic preschoolers and group cognitive behavior therapy for adults with high-functioning ASD
- Investigation on clinical evaluation and psychological education for adults with developmental disorders

References

1. Yagi T, Ando S, Usami S, Yamasaki S, Morita M, Kiyono T, Hayashi N, Endo K, Iijima Y, Morimoto Y, Kanata S, Fujikawa S, Koike S, Kano Y, Hiraiwa-Hasegawa M, Nishida A, Kasai K. Longitudinal Bidirectional Relationships Between Maternal Depressive/Anxious Symptoms and Children's Tic Frequency in Early Adolescence.Front Psychiatry, 12: 767571, 2021.
2. Kaji N, Ando S, Nishida A, Yamasaki S, Kuwabara H, Kanehara A, Satomura Y, Jinde S, Kano Y, Hiraiwa-Hasegawa M, Igarashi T, Kasai K. Children with special health care needs and mothers' anxiety/depression: Findings from the Tokyo Teen Cohort study. Psychiatry Clin Neurosci.,75(12): 394-400, 2021.
3. Eriguchi Y, Gu X, Aoki N, Nonaka M, Goto R, Kuwabara H, Kano Y, Kasai K. A 2-year longitudinal follow-up of quantitative assessment neck tics in Tourette's syndrome. PLoS One, 16(12): e0261560, 2021.
4. Okada N, Yamamoto Y, Yahata N, Morita S, Koshiyama D, Morita K, Sawada K, Kanata S, Fujikawa S, Sugimoto N, Toriyama R, Masaoka M, Koike S, Araki T, KanoY, Endo K, Yamasaki S, Ando S, Nishida A, Hiraiwa-Hasegawa M, Yokoyama C, Kasai K, Birth order and prosociality in the early adolescent brain. Sci Rep, 11(1): 21806, 2021.
5. Kimura Y, Iijima K, Takayama Y, Yokosako S, Kaneko Y, Omori M, Kaido T, Kano Y, Iwasaki M. Deep Brain Stimulation for Refractory Tourette Syndrome: Electrode Position and Clinical Outcome. Neurol Med Chir (Tokyo), 61(1): 33-39, 2021.
6. Kato Y, Kuwabara H, Okada T, Munesue T, Benner S, Kuroda M, Kojima M, Yassin W, Eriguchi Y, Kameno Y, Murayama C, Nishimura T, Tsuchiya K, Kasai K, Ozaki N, Kosaka H, Yamasue H. Oxytocin-induced increase in N,N-dimethylglycine and time course of changes in oxytocin efficacy for autism social core symptoms. Mol Autism, 12(1):15, 2021.
7. Kuru Y, Nishiyama T, Sumi S, Suzuki F, Shiino T, Kimura T, Hirai K, Kuroda M, Kamio Y, Kikuchi S. Practical applications of brief screening questionnaires for autism spectrum disorder in a psychiatry outpatient setting. Int J Methods Psychiatr Res, 30(2): e1857, 2021.

Neuroscience

3. Clinical Neuroscience

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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.

Clinical activities

For our clinical services, we have more than 20 staff psychiatrists, 5 clinical psychologists and 2 psychiatric social workers. In 2020, approximately 450 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. Approximately 330 patients with various psychiatric disorders were admitted in 2020. 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. The majority of the patients are schizophrenia, mood disorder and the psychosis based on the somatic diseases. Modified electroconvulsive therapy was performed for approximately 400 patients 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.

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. Echizen K, Sakakibara E, Suga M, Kasai K: Improvements in obsessive-compulsive disorder and schizophrenia after left putaminal hemorrhage. *Psychiatry Clin Neurosci*. 2021 Nov; 75(11):354-355.
2. ENIGMA Clinical High Risk for Psychosis Working Group,: Association of structural magnetic resonance imaging measures with psychosis onset in individuals at clinical high risk for developing psychosis: An ENIGMA Working Group mega-analysis. *JAMA Psychiatry* 78: 753-766, 2021. (Jul)
3. Furukawa Y, Saito H, Hasegawa K, Ichikawa M. Assessing the quality of cancer screening leaflets using the International Patient Decision Aids Standards instrument: A cross-sectional content analysis. *Patient Educ Couns*. 2021;104(12): 3100-3103. doi:10.1016/j.pec.2021.03.034
4. Ikegame T, Hidaka Y, Nakachi Y, Murata Y, Watanabe R, Sugawara H, Asai T, Kiyota E, Saito T, Ikeda M, Sasaki T, Hashimoto M, Ishikawa T, Takebayashi M, Iwata N, Kakiuchi C, Kato T, Kasai K, Bundo M, Iwamoto K: Identification and functional characterization of the extremely long allele of the serotonin transporter-linked polymorphic region. *Transl Psychiatry* 11: 119, 2021 (Feb).
5. Kaji N, Ando S, Nishida A, Yamasaki S, Kuwabara H, Kanehara A, Satomura Y, Jinde S, Kano Y, Hiraiwa-Hasegawa M, Igarashi T, Kasai K: Children with special health care needs and mothers' anxiety/depression: findings from the Tokyo Teen Cohort study. *Psychiatry Clin Neurosci*. 2021 Sep 22.
6. 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.
7. Koike S, Fujioka M, Satomura Y, Koshiyama D, Tada M, Sakakibara E, Okada N, Takano Y, Iwashiro N, Natsubori T, Zhu Y, Abe O, Kirihara

K, Yamasue H, Kasai K: Surface area in the insula was associated with 28-month functional outcome in first-episode psychosis. *NPJ Schizophr*. 2021 Nov 29;7(1):56.

8. Koike S, Fujioka M, Takano Y, Iwashiro N, Satomura Y, Nagai T, Koshiyama D, Tada M, Natsubori T, Okada N, Abe O, Kirihara K, Yamasue H, Suga M, Kasai K: Neurocognitive Deficits Mediate the Relationship Between Structural Abnormalities and Clinical Outcomes in Individuals With Ultrahigh Risk for Psychosis: A Multimodal Neuroimaging and Longitudinal Neurocognitive Study. *Schizophrenia Bulletin Open* 2, January 2021.
9. Koike S, Tanaka SC, Okada T, Aso T, Yamashita A, Yamashita O, Asano M, Maikusa N, Morita K, Okada N, Fukunaga M, Uematsu A, Togo H, Miyazaki A, Murata K, Urushibata Y, Autio J, Ose T, Yoshimoto J, Araki T, Glasser MF, Van Essen DC, Maruyama M, Sadato N, Kawato M, Kasai K, Okamoto Y, Hanakawa T, Hayashi T; Brain/MINDS Beyond Human Brain MRI Group. Brain/MINDS beyond human brain MRI project: A protocol for multi-level harmonization across brain disorders throughout the lifespan. *Neuroimage Clin* 30:102600, 2021. (Mar)
10. Koshiyama D, Miyakoshi M, Joshi YB, Molina JL, Tanaka-Koshiyama K, Sprock J, Braff DL, Swerdlow NR, Light GA. Neural network dynamics underlying gamma synchronization deficits in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 107:110224, 2021.
11. Koshiyama D, Miyakoshi M, Joshi YB, Nakanishi M, Tanaka-Koshiyama K, Sprock J, Light GA. Source decomposition of the frontocentral auditory steady-state gamma band response in schizophrenia patients and healthy subjects. *Psychiatry Clin Neurosci* 75: 172-279, 2021.
12. Koshiyama D, Miyakoshi M, Joshi YB, Nakanishi M, Tanaka-Koshiyama K, Sprock J, Light GA. Sources of the Frontocentral Mismatch Negativity and P3a Responses in Schizophrenia Patients and Healthy Comparison Subjects. *Int J Psychophysiol* 161:76-85, 2021.
13. Koshiyama D, Miyakoshi M, Tanaka-Koshiyama K, Joshi YB, Sprock J, Braff DL, Light GA. Abnormal phase discontinuity of alpha- and theta-frequency oscillations in schizophrenia. *Schizophr Res* 231: 73-81, 2021.
14. Koshiyama D, Miyakoshi M, Thomas ML, Joshi YB, Molina JL, Tanaka-Koshiyama K, Sprock J, Braff DL, Swerdlow NR, Light GA. Unique contributions of sensory discrimination and gamma synchronization deficits to cognitive, clinical, and psychosocial functional impairments in schizophrenia. *Schizophr Res* 228:280-287, 2021.
15. Koshiyama D, Thomas ML, Miyakoshi M, Joshi YB, Molina JL, Tanaka-Koshiyama K, Sprock J, Braff DL, Swerdlow NR, Light GA. Hierarchical pathways from sensory processing to cognitive, clinical, and functional impairments in schizophrenia. *Schizophr Bull* 47: 373-385, 2021.
16. 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*. 2021 May 22.
17. Nagaoka D, Tomoshige N, Ando S, Morita M, Kiyono T, Kanata S, Fujikawa S, Endo K, Yamasaki S, Fukuda M, Nishida A, Hiraiwa-Hasegawa M, Kasai K: Being praised for prosocial behaviors longitudinally reduces depressive symptoms in early adolescents: A population-based cohort study. *Front Psychiatry*. June 2021.
18. Okada N, Yamamoto Y, Yahata N, Morita S, Koshiyama D, Morita K, Sawada K, Kanata S, Fujikawa S, Sugimoto N, Toriyama R, Masaoka M, Koike S, Araki T, Kano Y, Endo K, Yamasaki S, Ando S, Nishida A, Hiraiwa-Hasegawa M, Yokoyama C, Kasai K: Birth order and prosociality in the early adolescent brain. *Sci Rep*. 2021 Nov 8;11(1):21806.
19. Sakakibara E, Satomura Y, Matsuoka J, Koike S, Okada N, Sakurada H, Yamagishi M, Kawakami N, Kasai K: Abnormality of Resting-State Functional Connectivity in Major Depressive Disorder: A Study With Whole-Head Near-Infrared Spectroscopy. *Front Psychiatry* 12: 664859, 2021. (Apr)

20. Tada M, Kirihara K, Ishishita Y, Takasago M, Kunii N, Uka T, Shimada S, Ibayashi K, Kawai K, Saito N, Koshiyama D, Fujioka M, Araki T, Kasai K: Global and parallel cortical processing based on auditory gamma oscillatory responses in humans. *Cereb Cortex*. 2021 Apr 28:bhab103.

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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 and dementia (Dementia center).

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 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, we have started a plan to conduct 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. (Toda, T., Kanagawa, M., Kobayashi, K., Sudo, A., Fujino, G., Kitamura, A., 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 atrophy, 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 expasions 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 adreno-leukodystrophy. We are now studying a biomarker for adrenoleukodystrophy. (Toda, T., Tsuji, S., Mitsui, J., Ishiura, H., Matsukawa, T., Naruse, H., Kakumoto, T., Nagasako, Y., Hao, A., Shinmi, J, Mitsue, A., Mitsutake, A., Yamaguchi, N., Almansour, M. A., 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 mismatch negativity changes in ataxic syndrome as well as basalganglia disorders and entrainment of neuronal oscillation by peripheral nerve stimulation, 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. (Hamada, M., Shirota, Y., Kodama, S., Kainaga M, Seto E, Katsuse K, Tokimura R, and Miyano R.)

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, muscle specific antibodies and para-neoplastic neurological antibodies. In research field, using biopsied muscles and collected serum samples, we have been studying the mechanisms of inflammatory myopathies from the view points 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. (Shimizu, J., Kubota A., Maeda M.).

In the biochemistry laboratory, autopsy brain analysis of Alzheimer's disease and Lewy body disease was performed, and a new gene involvement was discovered. Chronic cerebral hypoperfusion model mouse was created and its characteristics were analyzed, the technology was applied to analyze amyloid β metabolism under chromic hypoperfusion. On the other hand, we analyzed J-ADNI cohort data. Comparison with US-ADNI data revealed compatibility between the two cohorts. The influence of sex difference and education level, and the influence of serum calcium level was discovered. We analyzed the database of adverse drug reactions to COVID-19 vaccine and dementia drugs. Other activities include development of new imaging techniques using Raman microspectroscopy. We recently invented a novel high-sensitivity lipid imaging methodology using delipidation technique for sample preconditioning before Raman observation, which successfully determined spatial distribution of minor lipid species in porcine nerve and muscle tissues. We also developed a new optical sensor chip detecting biomarkers for Alzheimer's disease using nanoimprint lithography (NIL)-based two-dimensional photonic crystal (2D-PhC), which achieved the sensitivity surpassing ELISA. We newly developed a detection device for our sensor chip, realizing automated, high-throughput measurement. (Yu Nagashima, Ryo Ohtomo, Tatsuo Mano, Taro Bannai, Takeyuki Tsuchida, Kensuke Hamada, Kagari Mano, Gaku Ohtomo, Kenichiro Sato, Masanori Kurihara)

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. Yau WY, Vandrovcova J, Sullivan R, Chen Z, Zecchinelli A, Cilia R, Duga S, Murray M, Carmona S; Genomics England Research Consortium, Chelban V, Ishiura H, Tsuji S, Jaunmuktane Z, Turner C, Wood NW, Houlden H. Low Prevalence of NOTCH2NLC GGC Repeat Expansion in White Patients with Movement Disorders. ***Mov Disord***. 2021 Jan;36(1):251-255. doi: 10.1002/mds.28302.
2. Watanabe M, Nakamura Y, Sato S, Niino M, Fukaura H, Tanaka M, Ochi H, Kanda T, Takeshita Y, Yokota T, Nishida Y, Matsui M, Nagayama S, Kusunoki S, Miyamoto K, Mizuno M, Kawachi I, Saji E, Ohashi T, Shimohama S, Hisahara S, Nishiyama K, Iizuka T, Nakatsuji Y, Okuno T, Ochi K, Suzumura A, Yamamoto K, Kawano Y, Tsuji S, Hirata M, Sakate R, Kimura T, Shimizu Y, Nagaishi A, Okada K, Hayashi F, Sakoda A, Masaki K, Shinoda K, Isobe N, Matsushita T, Kira JI. HLA genotype-clinical phenotype correlations in multiple sclerosis and neuromyelitis optica spectrum disorders based on Japan MS/NMOSD Biobank data. ***Sci Rep***. 2021 Jan 12;11(1):607. doi: 10.1038/s41598-020-79833-7.

3. Kawai M, Mano T, Naito T, Honda A, Nakai Y, Toyama K, Fujioka Y, Makise N, Haesgawa H, Sakuishi K, Kurokawa M, **Toda T**. Disseminated necrotizing leukoencephalopathy after allogeneic peripheral blood stem cell transplantation and methotrexate administration. ***Neurol Clin Neurosci.*** 2021 Jan;9(1): 155-156.
4. Koh K, Takaki R, Ishiura H, Tsuji S, Takiyama Y. SPG9A with the new occurrence of an ALDH18A1 mutation in a CMT1A family with PMP22 duplication: case report. ***BMC Neurol***. 2021 Feb 11;21(1):64. doi: 10.1186/s12883-021-02087-x.
5. Naruse H, Ishiura H, Mitsui J, Takahashi Y, Matsukawa T, Yoshimura J, Doi K, Morishita S, Goto J, **Toda T**, Tsuji S. Loss-of-function variants in NEK1 are associated with an increased risk of sporadic ALS in the Japanese population. ***J Hum Genet.*** 2021 Mar;66(3):237-241. doi: 10.1038/ s10038-020-00830-9.
6. Song D, Dai Y, Chen X, Fu X, Chang X, Wang N, Zhang C, Yan C, Zheng H, Wu L, Jiang L, Hua Y, Yang H, Wang Z, Dai T, Zhu W, Han C, Yuan Y, Kobayashi K, **Toda T**, Xiong H. Genetic variations and clinical spectrum of dystroglycanopathy in a large cohort of Chinese patients. ***Clin Genet.*** 2021 Mar;99(3):384-395. doi: 10.1111/cge.13886.
7. Naruse H, Ishiura H, Mitsui J, Takahashi Y, Matsukawa T, Sakuishi K, Nakamagoe K, Miyake Z, Tamaoka A, Goto J, Yoshimura J, Doi K, Morishita S, **Toda T**, Tsuji S. Splice-site mutations in KIF5A in the Japanese case series of amyotrophic lateral sclerosis. ***Neurogenetics.*** 2021Mar;22(1):11-17. doi: 10.1007/s10048-020-00626-1.
8. Naito T, Suzuki K, Hirata J, Kamatani Y, Matsuda K, **Toda T**, Okada Y. A deep learning method for HLA imputation and trans-ethnic MHC fine-mapping of type 1 diabetes. ***Nat Comn*** 2021 Mar.12; 12(1)1639 doi:10.1038/s41467-021-21975-x.
9. Sato K, Ihara R, Suzuki K, Niimi Y, **Toda T**, Jimenez-Maggiora G, Langford O, Donohue MC, Raman R, Aisen PS, Sperling RA, Iwata A, Iwatsubo T. Predicting amyloid risk by machine learning algorithms based on the A4 screen data: Application to the Japanese Trial-Ready Cohort study. ***Alzheimers Dement (N Y).*** 2021 Mar 24; 7(1):e12135. doi: 10.1002/trc2.12135.
10. Miyazawa A, Kanahara N, Nakata Y, Kodama S, Kimura H, Kimura A, Oda Y, Watanabe H, Iyo M. Clozapine Prolongs Cortical Silent Period in Patients with Treatment-Resistant Schizophrenia. *Psychopharmacol Bull*. 2021 Mar 16;51(2):20 -30.
11. Taniguchi T, Ando M, Okamoto Y, Yoshimura A, Higuchi Y, Hashiguchi A, Shiga K, Hayashida A, Hatano T, Ishiura H, Mitsui J, Hattori N, Mizuno T, Nakagawa M, Tsuji S, Takashima H. Genetic spectrum of Charcot-Marie-Tooth disease associated with myelin protein zero gene variants in Japan. ***Clin Genet***. 2021 Mar;99(3):359-375. doi: 10.1111/cge.13881.
12. Okano A, Miyawaki S, Hongo H, Dofuku S, Teranishi Y, Mitsui J, Tanaka M, Shin M, Nakatomi H, Saito N. Associations of pathological diagnosis and genetic abnormalities in meningiomas with the embryological origins of the meninges. ***Sci Rep***. 2021 Mar 26;11(1): 6987. doi: 10.1038/s41598-021-86298-9.
13. Sato K, Mano T, Iwata A, **Toda T**. Disproportionality by sex in the prescription of drugs capable of inducing parkinsonism for the elderly: A survey using statistics of Japanese national health claims from 2014 to 2017. ***Neurology and Clinical Neuroscience.*** 2021 May: 9(3):211-217. doi:10.1111/ncn3.12501
14. Ueha R, Sato T, Goto T, Yamauchi A, Nativ-Zeltzer N, Mitsui J, Belafsky PC, Yamasoba T. Esophageal Dysmotility is Common in Patients With Multiple System Atrophy. ***Laryngoscope***. 2021 Apr; 131(4): 832-838. doi: 10.1002/lary. 28852.
15. Shibata Y, Matsushima M, Matsukawa T, Ishiura H, Tsuji S, Yabe I. Adrenoleukodystrophy siblings with a novel ABCD1 missense variant presenting with phenotypic differences: a case report and literature review. ***J Hum Genet***. 2021 May; 66(5): 535-537. doi: 10.1038/s10038-020-00866-x.
16. Hashimoto Y, Mitsui J, Ishiura H, Matsukawa T, **TodaT**, Kakisu K, Hori Y,Nakagawa S, Toyono T, Yoshida J, Usui T, Yamagami S, Aihara M, Miyai

T. A Case of Irreversible Corneal Edema Associated with Dentatorubropallidoluysian Atrophy Following Corneal Endothelial Transplantation. ***SN Comprehensive Clinical Medicine***. 2021 June5; 3: 2029-2032. doi:10.1007/s42399-021-00962-9

17. Mano T, Sato K, Ikeuchi T, **Toda T**, Iwatsubo T, Iwata A. Peripheral Blood BRCA1 Methylation Positively Correlates with Major Alzheimer's Disease Risk Factors. ***J Prev Alzheimers Dis.*** 2021June9; 8(4): 477-482. doi: 10.14283/jpad.2021.31.
18. Bonora E, Chakrabarty S, Kellaris G, Tsutsumi M, Bianco F, Bergamini C, Ullah F, Isidori F, Liparulo I, Diquigiovanni C, Masin L, Rizzardi N, Cratere MG, Boschetti E, Papa V, Maresca A, Cenacchi G, Casadio R, Martelli P, Matera I, Ceccherini I, Fato R, Raiola G, Arrigo S, Signa S, Sementa AR, Severino M, Striano P, Fiorillo C, Goto T, Uchino S, Oyazato Y, Nakamura H, Mishra SK, Yeh YS, Kato T, Nozu K, Tanboon J, Morioka I, Nishino I, **Toda T**, Goto YI, Ohtake A, Kosaki K, Yamaguchi Y, Nonaka I, Iijima K, Mimaki M, Kurahashi H, Raams A, MacInnes A, Alders M, Engelen M, Linthorst G, de Koning T, den Dunnen W, Dijkstra G, van Spaendonck K, van Gent DC, Aronica EM, Picco P, Carelli V, Seri M, Katsanis N, Duijkers FAM, Taniguchi-Ikeda M, De Giorgio R. Biallelic variants in LIG3 cause a novel mitochondrial neurogastrointestinal encephalomyopathy. ***Brain.*** 2021 June 22; 144(5): 1451-1466. doi: 10.1093/brain/ awab056.
19. Wiessner M, Maroofian R, Ni MY, Pedroni A, Müller JS, Stucka R, Beetz C, Efthymiou S, Santorelli FM, Alfares AA, Zhu C, Uhrova Meszarosova A, Alehabib E, Bakhtiari S, Janecke AR, Otero MG, Chen JYH, Peterson JT, Strom TM, De Jonghe P, Deconinck T, De Ridder W, De Winter J, Pasquariello R, Ricca I, Alfadhel M, van de Warrenburg BP, Portier R, Bergmann C, Ghasemi Firouzabadi S, Jin SC, Bilguvar K, Hamed S, Abdelhameed M, Haridy NA, Maqbool S, Rahman F, Anwar N, Carmichael J, Pagnamenta A, Wood NW, Tran Mau-Them F, Haack T; Genomics England Research Consortium, PREPARE network, Di Rocco M, Ceccherini I, Iacomino M, Zara F, Salpietro V, Scala M, Rusmini M, Xu Y, Wang Y, Suzuki Y, Koh K, Nan H, Ishiura H, Tsuji S, Lambert L, Schmitt E, Lacaze E, Küpper H, Dredge D, Skraban C, Goldstein A, Willis MJH, Grand K, Graham JM, Lewis RA, Millan F, Duman Ö, Dündar N, Uyanik G, Schöls L, Nürnberg P, Nürnberg G, Catala Bordes A, Seeman P, Kuchar M, Darvish H, Rebelo A, Bouçanova F, Medard JJ, Chrast R, Auer-Grumbach M, Alkuraya FS, Shamseldin H, Al Tala S, Rezazadeh Varaghchi J, Najafi M, Deschner S, Gläser D, Hüttel W, Kruer MC, Kamsteeg EJ, Takiyama Y, Züchner S, Baets J, Synofzik M, Schüle R, Horvath R, Houlden H, Bartesaghi L, Lee HJ, Ampatzis K, Pierson TM, Senderek J. Biallelic variants in HPDL cause pure and complicated hereditary spastic paraplegia. ***Brain***. 2021 Jun 22;144(5):1422-1434. doi: 10. 1093/brain/awab041.
20. Seike N, Yokoseki A, Takeuchi R, Saito K, Miyahara H, Miyashita A, Ikeda T, Aida I, Nakajima T, Kanazawa M, Wakabayashi M, Toyoshima Y, Takahashi H, Matsumoto R, **Toda T**, Onodera O, Ishikawa A, Ikeuchi T, Kakita A. Genetic Variations and Neuropathologic Features of Patients With PRKN Mutations. ***Mov Disord.*** 2021 Jul; 36(7): 1634-1643. doi: 10.1002/mds.28521.
21. Sato K, Mano T, Iwata A, **Toda T.** Need of care in interpreting Google Trends-based COVID-19 infodemiological study results: potential risk of false-positivity. ***BMC Med Res Methodol.*** 2021 Jul 18; 21(1):147. doi: 10.1186/s12874-021-01338-2.
22. Sato K, Niimi Y, Ihara R, Suzuki K, **Toda T**, Iwata A, Iwatsubo T. Efficacy and Cost-effectiveness of Promotion Methods to Recruit Participants to an Online Screening Registry for Alzheimer Disease Prevention Trials: Observational Study. ***J Med Internet Res.*** 2021 Jul 22;23(7):e26284. doi: 10.2196/26284.
23. Kumutpongpanich T, Ogasawara M, Ozaki A, Ishiura H, Tsuji S, Minami N, Hayashi S, Noguchi S, Iida A, Nishino I; OPDM_LRP12 Study Group, Mori-Yoshimura M, Oya Y, Ono K, Shimizu T, Kawata A, Shimohama S, Toyooka K, Endo K, Toru S, Sasaki O, Isahaya K, Takahashi MP, Iwasa K, Kira JI, Yamamoto T, Kawamoto M,

Hamano T, Sugie K, Eura N, Shiota T, Koide M, Sekiya K, Kishi H, Hideyama T, Kawai S, Yanagimoto S, Sato H, Arahata H, Murayama S, Saito K, Hara H, Kanda T, Yaguchi H, Imai N, Kawagashira Y, Sanada M, Obara K, Kaido M, Furuta M, Kurashige T, Hara W, Kuzume D, Yamamoto M, Tsugawa J, Kishida H, Ishizuka N, Morimoto K, Tsuji Y, Tsuneyama A, Matsuno A, Sasaki R, Tamakoshi D, Abe E, Yamada S, Uzawa A. Clinicopathologic Features of Oculopharyngodistal Myopathy With LRP12 CGG Repeat Expansions Compared With Other Oculopharyngodistal Myopathy Subtypes. ***JAMA Neurol***. 2021 Jul 1; 78(7): 853-863. doi: 10.1001/jamaneurol.2021.1509.

24. Sato K, Mano T, Ihara R, Suzuki K, Niimi Y, **Toda T**, Iwatsubo T, Iwata A. Cohort-Specific Optimization of Models Predicting Preclinical Alzheimer's Disease, to Enhance Screening Performance in the Middle of Preclinical Alzheimer's Disease Clinical Studies. ***J Prev Alzheimers Dis.*** 2021Aug 2;8(4):503-512. doi: 10.14283/jpad.2021.39.
25. Takeda N, Inuzuka R, Yagi H, Morita H, Ando M, Yamauchi H, Taniguchi Y, Porto KJ, Kanaya T, Ishiura H, Mitsui J, Tsuji S, **Toda T**, Ono M, Komuro I,Clinical Impact of Copy Number Variation on the Genetic Diagnosis of Syndromic Aortopathies.***Circ Genom Precis Med***. 2021 Aug; 14(4): e003458. doi: 10.1161/CIRCGEN.121.003458.
26. Naito T, Satake W, Ogawa K, Suzuki K, Hirata J, Foo JN, Tan EK, **Toda T**, Okada Y. Trans-Ethnic Fine-Mapping of the Major Histocompatibility Complex Region Linked to Parkinson's Disease. ***Mov Disord.*** 2021 Aug;36(8):1805-1814. doi: 10.1002/mds.28583.
27. Katsuse K, Kodama S, Okazaki K, Toda **T**. Delayed Brachial Plexus Palsy after Clavicular Fracture. ***Intern Med***. 2021 Aug 1;60(15):2511-2512. doi: 10.2169/internalmedicine.6988-20.
28. Chen XY, Song DY, Jiang L, Tan DD, Liu YD, Liu JY, Chang XZ, Xing GG, **Toda T**, Xiong H. Phenotype and Genotype Study of Chinese POMT2-Related α-Dystroglycanopathy. ***Front Genet.*** 2021 Aug 3; 12:692479. doi: 10.3389/fgene.2021.692479.
29. Sato K, Mano T, Iwata A, **Toda T.** Safety of Memantine in Combination with Potentially Interactive Drugs in the Real World: A Pharmacovigilance Study Using the Japanese Adverse Drug Event Report (JADER) Database. ***J Alzheimers Dis.*** 2021Aug 3; 82(3):1333-1344. doi: 10.3233/JAD-210524.
30. Ishigami D, Miyawaki S, Nakatomi H, Takayanagi S, Teranishi Y, Ohara K, Hongo H, Dofuku S, Kin T, Abe H, Mitsui J, Komura D, Katoh H, Ishikawa S, Saito N. Brainstem intraparenchymal schwannoma with genetic analysis: a case report and literature review. ***BMC Med Genomics***. 2021 Aug 18; 14(1): 205. doi: 10.1186/s12920-021-01049-z.
31. Taniguchi-Ikeda M, Koyanagi-Aoi M, Maruyama T, Takaori T, Hosoya A, Tezuka H, Nagase S, Ishihara T, Kadoshima T, Muguruma K, Ishigaki K, Sakurai H, Mizoguchi A, Novitch BG, **Toda T**, Watanabe M, Aoi T. Restoration of the defect in radial glial fiber migration and cortical plate organization in a brain organoid model of Fukuyama muscular dystrophy. ***iScience.*** 2021 Sep 17; 24(10):103140. doi: 10.1016/j.isci.2021.103140.
32. Sato K, Mano T, Niimi Y, Iwata A, **Toda T**, Iwatsubo T. The impact of COVID-19 pandemic on the utilization of ambulatory care for patients with chronic neurological diseases in Japan: Evaluation of an administrative claims database. ***Biosci Trends.*** 2021 Sep 22;15(4):219-230. doi: 10.5582/bst.2021.01194.
33. Kikuchi JK, Nagashima Y, Mano T, Ishiura H, Hayashi T, Shimizu J, Matsukawa T, Ichikawa Y, Takahashi Y, Karino S, Kanbayashi T, Kira J, Goto J, Tsuji S. Cerebellar Ataxia as a Common Clinical Presentation Associated with DNMT1 p.Y511H and a Review of the Literature. ***J Mol Neurosci***. 2021 Sep;71(9):1796-1801.
34. Sato K, Mano T, Niimi Y, **Toda T**, Iwata A, Iwatsubo T. Facial nerve palsy following the administration of COVID-19 mRNA vaccines: analysis of a self-reporting database. ***Int J Infect Dis.*** 2021 Oct;111:310-312. doi: 10.1016/j.ijid.2021.08.071.
35. Mitsutake A, Nagashima Y, Mori H, Sawamura H, **Toda T.** Paracentral homonymous hemianopic

scotoma caused by anterior choroidal artery infarction. ***QJM.*** 2021 Oct 7;114(6):417-418. doi: 10.1093/qjmed/hcab031.

36. Porto KJ, Hirano M, Mitsui J, Chikada A, Matsukawa T, Ishiura H; Japan Multiple System Atrophy Registry Consortium, **Toda T**, Kusunoki S, Tsuji S. COQ2 V393A confers high risk susceptibility for multiple system atrophy in East Asian population. ***J Neurol Sci.*** 2021 Oct 15; 429:117623. doi: 10.1016/j.jns.2021.117623.
37. Neshige S, Hitomi T, Tojima M, Oi K, Kobayashi K, Matsuhashi M, Shimotake A, Matsumoto R, Kanda M, Maruyama H, Ishiura H, Tsuji S, Takahashi R, Ikeda A. A Role of Aging in the Progression of Cortical Excitability in Benign Adult Familial Myoclonus Epilepsy type 1 Patients. ***Mov Disord***. 2021 Oct;36(10):2446-2448. doi: 10.1002/mds.28718.
38. Teranishi Y, Miyawaki S, Hongo H, Dofuku S, Okano A, Takayanagi S, Ota T, Yoshimura J, Qu W, Mitsui J, Nakatomi H, Morishita S, Tsuji S, Saito N. Targeted deep sequencing of DNA from multiple tissue types improves the diagnostic rate and reveals a highly diverse phenotype of mosaic neurofibromatosis type 2. ***J Med Genet***. 2021 Oct; 58(10):701-711. doi: 10.1136/jmedgenet-2020-106973.
39. Kainaga M, Shirota Y, Kodama S, **Toda T**, Hamada M. Effects of the Coronavirus Disease 2019 Pandemic on Motor Symptoms in Parkinson's Disease: An Observational Study. ***Mov Disord***. 2021 Nov;36(11):2461-2463. doi: 10.1002/mds.28766.
40. Kakumoto T, Kobayashi S, Yuuki H, Kainaga M, Shirota Y, Hamada M, Hashimoto Maeda M, Kubota A, Kawai M, Saito M, Ishiura H, **Toda T**. Cranial Nerve Involvement and Dysautonomia in Post-COVID-19 Guillain-Barré Syndrome. ***Intern Med***. 2021 Nov 1;60(21): 3477-3480. doi: 10.2169/internalmedicine.7355-21.
41. Mitsutake A, Unuma A, Kawai M, Kubota A, Ishiura H, Sakuishi K, Shimizu J, Maki H, Amiya E, Hatano M, Komuro I, Tsuji S, **Toda T**. Severe dilated cardiomyopathy and ventricular arrhythmia in a Patient with Emery-Dreifuss muscular dystrophy harboring a novel frameshift mutation in EMD. ***Neurol Clin Neurosci***. 2021 Nov;9:490-493.doi:10.1111/ncn3.12552
42. Almansour A, Ishiura H, Mitsui J, Matsukawa T, Matsukawa MK, Shimizu H, Sugiyama A, **Toda T**, Tsuji S. Frequency of FMR1 Premutation Alleles in Patients with Undiagnosed Cerebellar Ataxia and Multiple System Atrophy in the Japanese Population.***Cerebellum***. 2021 Nov 29. doi: 10. 1007/s12311-021-01329-5.
43. Naruse H, Ishiura H, Mitsui J, Takahashi Y, Matsukawa T, Toda T, Tsuji S. Juvenile amyotrophic lateral sclerosis with complex phenotypes associated with novel SYNE1 mutations. ***Amyotroph Lateral Scler Frontotemporal Degener***. 2021 Nov;22(7-8): 576-578. doi: 10.1080/21678421.2020.1813312.
44. Mochizuki H, Aoki M, Ikenaka K, Inoue H, Iwatsubo T, Ugawa Y, Okazawa H, Ono K, Onodera O, Kitagawa K, Saito Y, Shimohata T, Takahashi R, **Toda T**, Nakahara J, Matsumoto R, Mizusawa H, Mitsui J, Murayama S, Katsuno M; Future Vision Committee of Japanese Society of Neurology, Aoki Y, Ishiura H, Izumi Y, Koike H, Shimada H, Takahashi Y, Tokuda T, Nakajima H, Hatano T, Misawa S, Watanabe H. [Recommendations (Proposal) for promoting research for overcoming neurological diseases 2020]. ***Rinsho Shinkeigaku***. 2021 Nov 24; 61(11): 709-721. doi: 10.5692/clinicalneurol.cn-001639.
45. Kuroda N, Kubota T, Horinouchi T, Ikegaya N, Kitazawa Y, Kodama S, Matsubara T, Nagino N, Neshige S, Soga T, Sone D, Takayama Y, Kuramochi I; IMPACT-J EPILEPSY (In-depth Multicenter analysis during Pandemic of Covid19 Throughout Japan for Epilepsy practice) study group. Risk factors for psychological distress in electroencephalography technicians during the COVID-19 pandemic: A national-level cross-sectional survey in Japan. ***Epilepsy Behav***. 2021 Dec; 125: 108361. doi: 10.1016/j.yebeh.2021.108361.
46. Watanabe N, Nakano M, Mitsuishi Y, Hara N, Mano T, Iwata A, Murayama S, Suzuki T, Ikeuchi T, Nishimura M. Transcriptional downregulation of FAM3C/ILEI in the Alzheimer's brain. ***Hum Mol Genet***. 2021 Dec 17;31(1):122-132. doi: 10.1093/hmg/ddab226.

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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 2020 to March 2020, 16,509 patients were treated at the outpatient clinics.

The neurosurgery ward has approximately 40 beds on the seventh floor of the new hospital building opened in September 2001. In 2020, 791 patients were admitted to the neurosurgery ward. 386 surgical procedures and 204 gamma knife procedures were performed in 2020. Our practice covers a wide variety of neurosurgical diseases including malignant and benign brain tumors, hemorrhagic and thrombo-embolic cerebrovascular diseases, spinal disorders, 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. 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 35 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 11,500 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 4 in 2016, 16 in 2017, 5 in 2018, 7 in 2019, 9 in 2020 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) Pathogenesis of cerebral ischemia and neuronal regeneration after ischemic brain damage

One of the major topics in recent basic science is to regenerate the brain with endogenous neural progenitors. Our laboratory has started basic research to regenerate neurons in vivo following ischemic insult. We have demonstrated that the 40% of the lost neurons could be regenerated by administration of growth factors. We also succeeded in regeneration of striatal neurons. Molecular mechanisms of adult neurogenesis are currently investigated using various models to enhance post-ischemic regeneration. By extending the research into primate model, we are pursuing clinical application in the future.

2) 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 disese, *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 diseae 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.

3) 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 analysisng surgically resected tumor specimens in a semi-prospective fashion. The genetic analyses includes sequencing of *IDH1/2* and histone 3-coding genes, as well as loss of heterozygosity analysis of 1p, 19q, and 10q, and methylation analysis of *MGMT* promotor. We optimize therapy based upon the results of the above genetic analyses. In addition, we have been searching for novel biomarkers and therapeutic targets using comprehesive genetic and epigenetic analyses with whole exome sequencing, RNA sequencing, 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 are ongoing.

We have been collaborating with a basic research lab in our university and developing novel fluorescence probes specifically detecting glioma with a hope that fluorescence-guided surgery may result in greater extent of resection.

4) 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.

5) 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.

6) 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 multi-modalities 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.

7) 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 taking 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 (2021)

1. Amemiya S., Watanabe Y., Takei N., Ueyama T., Miyawaki S., Koizumi S., Kato S., Takao H., Abe O., Saito N. Reliability and Sensitivity to Longitudinal CBF Changes in Steno-Occlusive Diseases: ASL Versus (123) I-IMP-SPECT. **J Magn Reson Imaging**, 2021 doi: 10.1002/jmri.27996
2. Amemiya S., Watanabe Y., Takei N., Ueyama T., Miyawaki S., Koizumi S., Kato S., Takao H., Abe O., Saito N. Arterial Transit Time-Based Multidelay Combination Strategy Improves Arterial Spin Labeling Cerebral Blood Flow Measurement Accuracy in Severe Steno-Occlusive Diseases. **J Magn Reson Imaging**, 2021 doi: 10.1002/jmri.27823
3. Aono T., Shinya Y., Miyawaki S., Sugiyama T., Kumagai I., Takenobu A., Shin M., Saito N., Teraoka A. Changes in the Risk of Stroke in Dialysis Patients: A Retrospective Analysis over the Last 40 Years. **Toxins** 13(5), 2021 doi: 10.3390/toxins13050350
4. Fukushima Y., Uchida S., Imai H., Nakatomi H., Kataoka K., Saito N., Itaka K. Treatment of ischemic neuronal death by introducing brain-derived neurotrophic factor mRNA using polyplex nanomicelle. **Biomaterials** 270:120681, 2021 doi: 10.1016/j.biomaterials.2021.120681
5. Hasegawa H., Kin T., Shin M., Suzuki Y., Kawashima M., Shinya Y., Shiode T., Nakatomi H., Saito N. Possible Association Between Rupture and Intranidal Microhemodynamics in

Arteriovenous Malformations: Phase-Contrast Magnetic Resonance Angiography-Based Flow Quantification. **World Neurosurg** 150:e427-e435, 2021 doi: 10.1016/j.wneu.2021.03.036

6. Hirano Y., Miyawaki S., Imai H., Hongo H., Teranishi Y., Dofuku S., Ishigami D., Ohara K., Koizumi S., Ono H., Nakatomi H., Saito N. Differences in Clinical Features among Different Onset Patterns in Moyamoya Disease. **Journal of clinical medicine** 10(13), 2021 doi: 10.3390/jcm10132815
7. Hirano Y., Miyawaki S., Tanaka S., Taoka K., Hongo H., Teranishi Y., Takami H., Takayanagi S., Kurokawa M., Saito N. Clinical Features and Prognostic Factors for Primary Anaplastic Large Cell Lymphoma of the Central Nervous System: A Systematic Review. **Cancers** 13(17), 2021 doi: 10.3390/cancers13174358
8. Hirata T., Miyawaki S., Koizumi S., Teranishi Y., Ishikawa O., Saito N. Spontaneous regression of a symptomatic developmental venous anomaly with capillary stain. **Interventional neuroradiology : journal of peritherapeutic neuroradiology, surgical procedures and related neurosciences**:15910199211032470, 2021 doi: 10.1177/15910199211032470
9. Hong S., Hasegawa H., Shin M., Shinya Y., Saito N. Endoscopic Transsphenoidal Resection of Suprasellar Histiocytosis in a Patient with Erdheim-Chester Disease: A Case Report. **NMC case report journal** 8(1):117-122, 2021 doi: 10.2176/nmccrj.cr.2020-0126
10. Iihara K., Saito N., Suzuki M., Date I., Fujii Y., Houkin K., Inoue T., Iwama T., Kawamata T., Kim P., Kinouchi H., Kishima H., Kohmura E., Kurisu K., Maruyama K., Matsumaru Y., Mikuni N., Miyamoto S., Morita A., Nakase H., Narita Y., Nishikawa R., Nozaki K., Ogasawara K., Ohata K., Sakai N., Sakamoto H., Shiokawa Y., Takahashi J. C., Ueki K., Wakabayashi T., Yoshimoto K., Arai H., Tominaga T. The Japan Neurosurgical Database: Statistics Update 2018 and 2019. **Neurol Med Chir (Tokyo)**, 2021 doi: 10.2176/nmc.st.2021-0254
11. Ishigami D., Koizumi S., Ishikawa O., Toshimitsu M., Iriyama T., Miyawaki S., Saito N. Embolization of dural arteriovenous fistula during twin pregnancy - A case report and literature review. **Interventional neuroradiology : journal of peritherapeutic neuroradiology, surgical procedures and related neurosciences** 27(5):658-662, 2021 doi: 10.1177/1591019921991396
12. Ishigami D., Miyawaki S., Imai H., Shimizu M., Hongo H., Dofuku S., Ohara K., Teranishi Y., Shimada D., Koizumi S., Ono H., Hirano Y., Segawa M., Nakatomi H., Saito N. Correction to: RNF213 p.Arg4810Lys Heterozygosity in Moyamoya Disease Indicates Early Onset and Bilateral Cerebrovascular Events. **Translational stroke research**, 2021 doi: 10.1007/s12975-021-00971-9
13. Ishigami D., Miyawaki S., Nakatomi H., Takayanagi S., Teranishi Y., Ohara K., Hongo H., Dofuku S., Kin T., Abe H., Mitsui J., Komura D., Katoh H., Ishikawa S., Saito N. Brainstem intraparenchymal schwannoma with genetic analysis: a case report and literature review. **BMC medical genomics** 14(1):205, 2021 doi: 10.1186/s12920-021-01049-z
14. Kawashima M., Hasegawa H., Shin M., Shinya Y., Katano A., Saito N. Outcomes of stereotactic radiosurgery in young adults with vestibular schwannomas. **J Neurooncol** 154(1):93-100, 2021 doi: 10.1007/s11060-021-03803-w
15. Kawashima M., Hasegawa H., Shin M., Shinya Y., Saito N. Intratumoral hemorrhage in jugular foramen schwannoma after stereotactic radiosurgery: A case report. **Surg Neurol Int** 12:479, 2021 doi: 10.25259/sni_550_2021
16. Kitagawa Y., Tanaka S., Kamiya M., Kuriki Y., Yamamoto K., Shimizu T., Nejo T., Hana T., Matsuura R., Koike T., Yamazawa E., Kushihara Y., Takahashi S., Nomura M., Takami H., Takayanagi S., Mukasa A., Urano Y., Saito N. A Novel Topical Fluorescent Probe for Detection of Glioblastoma. **Clin Cancer Res** 27(14):3936-3947, 2021 doi: 10.1158/1078-0432.ccr-20-4518
17. Kiyofuji S., Kin T., Kakizawa Y., Doke T., Masuda T., Yamashita J., Shono N., Nakatomi H., Morita A., Harada K., Saito N. Development of Integrated 3-Dimensional Computer Graphics Human Head Model. **Operative neurosurgery (Hagerstown, Md)** 20(6):565-574, 2021 doi:

10.1093/ons/opab012

18. Koike T., Kin T., Tanaka S., Sato K., Uchida T., Takeda Y., Uchikawa H., Kiyofuji S., Saito T., Takami H., Takayanagi S., Mukasa A., Oyama H., Saito N. Development of a New Image-Guided Neuronavigation System: Mixed-Reality Projection Mapping Is Accurate and Feasible. **Operative neurosurgery (Hagerstown, Md)** 21(6):549-557, 2021 doi: 10.1093/ons/opab353
19. Koike T., Kin T., Tanaka S., Takeda Y., Uchikawa H., Shiode T., Saito T., Takami H., Takayanagi S., Mukasa A., Oyama H., Saito N. Development of Innovative Neurosurgical Operation Support Method Using Mixed-Reality Computer Graphics. **World neurosurgery: X** 11:100102, 2021 doi: 10.1016/j.wnsx.2021.100102
20. Koizumi S., Shojima M., Dofuku S., Saito A., Nomura S., Ono H., Ishikawa O., Saito N. Neuroendovascular Training Using Multisource Video-Recording System in a Hybrid Operating Room. **World Neurosurg** 154:e320-e324, 2021 doi: 10.1016/j.wneu.2021.07.029
21. Kunii N., Koizumi T., Kawai K., Shimada S., Saito N. Vagus Nerve Stimulation Amplifies Task-Induced Cerebral Blood Flow Increase. **Frontiers in human neuroscience** 15:726087, 2021 doi: 10.3389/fnhum.2021.726087
22. Nomura S K. T., Kunimatsu A, Shojima M, Watanebe Y, Suzuki Y, Shono N, Imai H, Saito T, Nakatomi H, Oyama H, Saito N. . Registration Method Between Phase-Contrast Magnetic Resonance Angiography and Time-of-Flight Magnetic Resonance Angiography—A Preliminary Study. **Journal of Medical Imaging and Health Informatics** 11(1):33-39, 2021 doi: https://doi.org/10.1166/jmihi.2021.3505
23. Noyama T., Katano A., Shinya Y., Kawashima M., Shin M., Saito N., Yamashita H. Prognostic Factors for Patients With Brain Metastases Treated With Single-fraction Gamma Knife Radiosurgery. **Anticancer Res** 41(6):3179-3185, 2021 doi: 10.21873/anticanres.15104
24. Okano A., Miyawaki S., Hongo H., Dofuku S., Teranishi Y., Mitsui J., Tanaka M., Shin M., Nakatomi H., Saito N. Associations of pathological diagnosis and genetic abnormalities in meningiomas with the embryological origins of the meninges. **Sci Rep** 11(1):6987, 2021 doi: 10.1038/s41598-021-86298-9
25. Oya S., Takayanagi S., Takami H., Indo M., Yamashita T., Saito N., Matsui T. Masked malignant phenotype with a benign appearance: beat-up copy number profile may be the key for hemangioblastoma dissemination. **Brain Tumor Pathol** 38(1):71-77, 2021 doi: 10.1007/s10014-020-00387-7
26. Saito N., Kobayashi Y., Nagaoka K., Kushihara Y., Sato Y., Wada I., Kakimi K., Seto Y. Two distinct phenotypes of immunologically hot gastric cancer subtypes. **Biochemistry and biophysics reports** 28:101167, 2021 doi: 10.1016/j.bbrep.2021.101167
27. Sato D., Hasegawa H., Shin M., Kondo K., Saito N. Combined endoscopic endonasal transtubercular and transclival approaches for large neurenteric cyst in posterior cranial fossa: A case report and literature review. **Surg Neurol Int** 12:554, 2021 doi: 10.25259/sni_648_2021
28. Satomi K., Takami H., Fukushima S., Yamashita S., Matsushita Y., Nakazato Y., Suzuki T., Tanaka S., Mukasa A., Saito N., Kanamori M., Kumabe T., Tominaga T., Kobayashi K., Nagane M., Iuchi T., Yoshimoto K., Tamura K., Maehara T., Sakai K., Sugiyama K., Yokogami K., Takeshima H., Nonaka M., Asai A., Ushijima T., Matsutani M., Nishikawa R., Ichimura K. 12p gain is predominantly observed in non-germinomatous germ cell tumors and identifies an unfavorable subgroup of central nervous system germ cell tumors. **Neuro Oncol**, 2021 doi: 10.1093/neuonc/noab246
29. Shinya Y., Hasegawa H., Kawashima M., Shin M., Takahashi W., Kobayashi H., Saito N. Stereotactic radiosurgery as a primary treatment for metastatic skull base alveolar soft part sarcoma: a case report. **Acta Neurochir (Wien)** 163(2):351-355, 2021 doi: 10.1007/s00701-020-04496-2
30. Shinya Y., Hasegawa H., Shin M., Kawashima M., Sugiyama T., Ishikawa O., Koizumi S., Suzuki Y., Nakatomi H., Saito N. Rotational Angiography-Based Gamma Knife Radiosurgery for Brain Arteriovenous Malformations: Preliminary Therapeutic Outcomes of the Novel Method.

Neurosurgery 89(1):60-69, 2021 doi: 10.1093/neuros/nyab066

31. Shinya Y., Hasegawa H., Shin M., Sugiyama T., Kawashima M., Katano A., Kashio A., Kondo K., Saito N. Long-Term Outcomes of Stereotactic Radiosurgery for Trigeminal, Facial, and Jugular Foramen Schwannoma in Comparison with Vestibular Schwannoma. **Cancers** 13(5), 2021 doi: 10.3390/cancers13051140
32. Sugino T., Kawase T., Onogi S., Kin T., Saito N., Nakajima Y. Loss Weightings for Improving Imbalanced Brain Structure Segmentation Using Fully Convolutional Networks. **Healthcare (Basel, Switzerland)** 9(8), 2021 doi: 10.3390/healthcare9080938
33. Sugino T., Roth H. R., Oda M., Kin T., Saito N., Nakajima Y., Mori K. Performance improvement of weakly supervised fully convolutional networks by skip connections for brain structure segmentation. **Medical physics** 48(11):7215-7227, 2021 doi: 10.1002/mp.15192
34. Sugino T., Suzuki Y., Kin T., Saito N., Onogi S., Kawase T., Mori K., Nakajima Y. Label cleaning and propagation for improved segmentation performance using fully convolutional networks. **Int J Comput Assist Radiol Surg** 16(3):349-361, 2021 doi: 10.1007/s11548-021-02312-5
35. Tada M., Kirihara K., Ishishita Y., Takasago M., Kunii N., Uka T., Shimada S., Ibayashi K., Kawai K., Saito N., Koshiyama D., Fujioka M., Araki T., Kasai K. Global and Parallel Cortical Processing Based on Auditory Gamma Oscillatory Responses in Humans. **Cereb Cortex** 31(10):4518-4532, 2021 doi: 10.1093/cercor/bhab103
36. Takabatake K., Kunii N., Nakatomi H., Shimada S., Yanai K., Takasago M., Saito N. Musical Auditory Alpha Wave Neurofeedback: Validation and Cognitive Perspectives. **Applied psychophysiology and biofeedback** 46(4):323-334, 2021 doi: 10.1007/s10484-021-09507-1
37. Takahashi S., Takahashi M., Kinoshita M., Miyake M., Kawaguchi R., Shinojima N., Mukasa A., Saito K., Nagane M., Otani R., Higuchi F., Tanaka S., Hata N., Tamura K., Tateishi K., Nishikawa R., Arita H., Nonaka M., Uda T., Fukai J., Okita Y., Tsuyuguchi N., Kanemura Y., Kobayashi K., Sese J., Ichimura K., Narita Y., Hamamoto R. Fine-Tuning Approach for Segmentation of Gliomas in Brain Magnetic Resonance Images with a Machine Learning Method to Normalize Image Differences among Facilities. **Cancers** 13(6), 2021 doi: 10.3390/cancers13061415
38. Takami H., Graffeo C. S., Perry A., Ohno M., Ishida J., Giannini C., Narita Y., Nakazato Y., Saito N., Nishikawa R., Matsutani M., Ichimura K., Daniels D. J. Histopathology and prognosis of germ cell tumors metastatic to brain: cohort study. **J Neurooncol** 154(1):121-130, 2021 doi: 10.1007/s11060-021-03810-x
39. Takami H., Satomi K., Fukuoka K., Fukushima S., Matsushita Y., Yamasaki K., Nakamura T., Tanaka S., Mukasa A., Saito N., Suzuki T., Yanagisawa T., Nakamura H., Sugiyama K., Tamura K., Maehara T., Nakada M., Nonaka M., Asai A., Yokogami K., Takeshima H., Iuchi T., Kanemura Y., Kobayashi K., Nagane M., Kurozumi K., Yoshimoto K., Matsuda M., Matsumura A., Hirose Y., Tokuyama T., Kumabe T., Narita Y., Shibui S., Nakazato Y., Nishikawa R., Matsutani M., Ichimura K. Low tumor cell content predicts favorable prognosis in germinoma patients. **Neuro-oncology advances** 3(1):vdab110, 2021 doi: 10.1093/noajnl/vdab110
40. 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**:1-3, 2021 doi: 10.1080/02688697.2021.1927982
41. Takeda Y., Kin T., Sekine T., Hasegawa H., Suzuki Y., Uchikawa H., Koike T., Kiyofuji S., Shinya Y., Kawashima M., Saito N. Hemodynamic Analysis of Cerebral AVMs with 3D Phase-Contrast MR Imaging. **AJNR Am J Neuroradiol** 42(12):2138-2145, 2021 doi: 10.3174/ajnr.A7314
42. Tanabe R., Miyazono K., Todo T., Saito N., Iwata C., Komuro A., Sakai S., Raja E., Koinuma D., Morikawa M., Westermark B., Heldin C. H. PRRX1 induced by BMP signaling decreases tumorigenesis by epigenetically regulating glioma-initiating cell properties via DNA

methyltransferase 3A. **Molecular oncology**, 2021 doi: 10.1002/1878-0261.13051

43. Tanaka H., Lee H., Morita A., Namkoong H., Chubachi S., Kabata H., Kamata H., Ishii M., Hasegawa N., Harada N., Ueda T., Ueda S., Ishiguro T., Arimura K., Saito F., Yoshiyama T., Nakano Y., Mutoh Y., Suzuki Y., Murakami K., Okada Y., Koike R., Kitagawa Y., Tokunaga K., Kimura A., Imoto S., Miyano S., Ogawa S., Kanai T., Fukunaga K. Clinical Characteristics of Patients with Coronavirus Disease (COVID-19): Preliminary Baseline Report of Japan COVID-19 Task Force, a Nationwide Consortium to Investigate Host Genetics of COVID-19. **International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases** 113:74-81, 2021 doi: 10.1016/j.ijid.2021.09.070
44. Teranishi Y., Miyawaki S., Hongo H., Dofuku S., Okano A., Takayanagi S., Ota T., Yoshimura J., Qu W., Mitsui J., Nakatomi H., Morishita S., Tsuji S., Saito N. Targeted deep sequencing of DNA from multiple tissue types improves the diagnostic rate and reveals a highly diverse phenotype of mosaic neurofibromatosis type 2. **Journal of medical genetics** 58(10):701-711, 2021 doi: 10.1136/jmedgenet-2020-106973
45. Tsuchiya T., Koizumi S., Tomioka A., Miyawaki S., Saito N. Acute Ischemic Stroke Due to Basilar Artery Occlusion with Coronavirus Disease 2019: A Case Report. **NMC case report journal** 8(1):579-585, 2021 doi: 10.2176/nmccrj.cr.2021-0043
46. Tsunoda S., Inoue T., Ohwaki K., Akabane A., Saito N. Comparison of postoperative temporalis muscle atrophy between the muscle-preserving pterional approach and the mini-pterional approach in the treatment of unruptured intracranial aneurysms. **Neurosurg Rev**, 2021 doi: 10.1007/s10143-021-01558-6
47. Uchida T., Kin T., Koike T., Kiyofuji S., Uchikawa H., Takeda Y., Miyawaki S., Nakatomi H., Saito N. Identification of the Facial Colliculus in Two-dimensional and Three-dimensional Images. **Neurol Med Chir (Tokyo)** 61(6):376-384, 2021 doi: 10.2176/nmc.oa.2020-0417
48. Uchikawa H., Kin T., Takeda Y., Koike T., Kiyofuji S., Koizumi S., Shiode T., Suzuki Y., Miyawaki S., Nakatomi H., Mukasa A., Saito N. Correlation of Inflow Velocity Ratio Detected by Phase Contrast Magnetic Resonance Angiography with the Bleb Color of Unruptured Intracranial Aneurysms. **World neurosurgery: X** 10:100098, 2021 doi: 10.1016/j.wnsx.2021.100098

Social Medicine

1. Occupational, Environmental and Preventive Medicine

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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) 9 students (1 are from outside of UTokyo), 2 technical staffs, 7 technical assistants, 1 collaboration researcher, 3 visiting researchers, 1 academic support staff, and 1 project specialist. Also, three collaborative researchers from private companies have joined our laboratory.

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. 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. Through our lectures and practical courses in “Preventive Medicine”, students learn the concept of preventive medicine.

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-ethic 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.

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

As the volume of available biomedical information is growing rapidly, technology to extract essential abstract information by compressing dimensions of an enormous amount of biological data is extremely important in our society. In the department of Preventive Medicine, deep neural network is applied to extract essential information (deep texture) of cancer from cancer histopathological images. Our goal is to develop tools to achieve a uniform pathological

diagnosis and to help eliminate regional medical care disparities. We developed Luigi, a content-based image retrieval system for cancer histopathological images, and made it available to pathologists and researchers in Web (https://luigi-pathology.com/) and smartphone application. The database in Luigi contains histopathologial images and their deep texture from more than 7,000 cases of 32 cancer types in The Cancer Genome Atlas. By uploading images, histopathological similar cases in the database are presented. Currently, we're trying to expand the Luigi database by collaborating with various hospitals. We also focus on the development of contents which would seamlessly connect routine lab tests performed in small clinics and cancer genome medicine given in large core hospitals by integrated analysis of histopathological information and cancer genome information.

Publications

1. Sueyoshi, K., Komura, D., Katoh, H., Yamamoto, A., Onoyama, T., Chijiwa, T., Isagawa, T., Tanaka, M., Suemizu, H., Nakamura, M., Miyagi, Y., Aburatani, H., Ishikawa, S., 2021. Multi-tumor analysis of cancer-stroma interactomes of patient-derived xenografts unveils the unique homeostatic process in renal cell carcinomas. **iScience** 24, 103322.
2. Ishigami, D., Miyawaki, S., Nakatomi, H., Takayanagi, S., Teranishi, Y., Ohara, K., Hongo, H., Dofuku, S., Kin, T., Abe, H., Mitsui, J., Komura, D., Katoh, H., Ishikawa, S., Saito, N., 2021. Brainstem intraparenchymal schwannoma with genetic analysis: a case report and literature review. **BMC Med Genomics** 14, 205.
3. Komura, D., Ishikawa, S., 2021. Advanced deep learning applications in diagnostic pathology. **Translational and Regulatory Sciences** 3, 36–42.
4. Katoh, H., Ishikawa, S., 2021. Lifestyles, genetics, and future perspectives on gastric cancer in east Asian populations. **J Hum Genet** 66, 887–899.
5. Imai, S., Ooki, T., Murata-Kamiya, N., Komura, D., Tahmina, K., Wu, W., Takahashi-Kanemitsu, A., Knight, C.T., Kunita, A., Suzuki, N., Del Valle, A.A., Tsuboi, M., Hata, M., Hayakawa, Y., Ohnishi, N., Ueda, K., Fukayama, M., Ushiku, T., Ishikawa, S., Hatakeyama, M., 2021. Helicobacter pylori CagA elicits BRCAness to induce genome instability that may underlie bacterial gastric carcinogenesis. **Cell Host Microbe** 29, 941-958.e10.
6. Ohkuma, R., Yada, E., Ishikawa, S., Komura, D., Kubota, Y., Hamada, K., Horiike, A., Ishiguro, T., Hirasawa, Y., Ariizumi, H., Shida, M., Watanabe, M., Onoue, R., Ando, K., Tsurutani, J., Yoshimura, K., Sasada, T., Aoki, T., Murakami, M., Norose, T., Ohike, N., Takimoto, M., Kobayashi, S., Tsunoda, T., Wada, S., 2021. High levels of human epididymis protein 4 mRNA and protein expression are associated with chemoresistance and a poor prognosis in pancreatic cancer. **Int J Oncol** 58, 57–69.

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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 5 faculty members above listed, 2 project researchers (part-time), 2 supporting staff members, 6

graduate students (3 in PhD program, 3 in professional degree course), 16 part-time lecturers, and 31 visiting fellows.

Teaching activities

1) Undergraduate Program (Medical School)

In 2020, because of the COVID-19 pandemic, all the lectures as well as field practice and laboratory work were conducted online. In the Autumn term of the fourth grade in School of Medicine (M2), students are provided with the following lectures; current issues of public health, preventive services, epidemiology, clinical epidemiology, quality of care, health economics, community medicine, infectious diseases and tuberculosis control, mental health, human ecology, global health, non-communicable diseases prevention and management, disaster public health, and so on. Similarly, in the sixth grade (M4), an intensive course of public health (e.g., health care systems, current health policy, occupational and environmental health, nutritional epidemiology, physical activity and health, and health services research) is provided. All the above lectures are given by faculty members and part-time lectures including health practitioners.

Field practice and laboratory work in public health is due in the summer term of the fifth grade (M3), which is jointly provided by Department of Preventive Medicine and the other departments related to public health fields. Averagely four to five students (small group) are assigned to one special topic group with a tutor (faculty member or part-time lecturer; we had 18 groups this year). Each group conducts field practice, review work, or laboratory work, and writes a report in the style of original or review paper.

The Department provides those lectures related to public health and occupational medicine for undergraduate students in the School of Integrated Health Sciences, Faculty of Arts and Sciences, and Faculty of Engineering. The Department also provides part of the course for those graduate students in Graduate School of Public Policy and the GSDM program.

2) MPH Program

Various courses (more than 40 courses) are given by those departments affiliated with School of Public Health. Among them, our Department offers three courses; “Health Policy”, “Public Health Preparedness”, and “Public Health Practice”.

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.

Research activities

1) Health policy and economics

Our research activities focus on the topics of health care system and economics in general. We have performed and published those studies related to supply and demand sides of health services in Japan; such as supply and distribution of physicians, access to health care, cost studies of outpatient and inpatient services, and the efficiency and equity issues of the Japan's health insurance system as well as universal health coverage system. We also conduct research on quality of care and social determinants of health. These studies have been published in health policy and health services research journals. We have continued a collaborative study on UHC systems both in developed and developing countries, since such a system involves health, behavioral, social, and economic factors, and would inevitably be an important health policy issue.

2) Occupational health

We have carried on a longitudinal study on life-style, socio-economic status, occupational stress, and health status of workers in various occupational settings for the purpose of preventing occupational and life-style diseases.

3) Others

Other research activities include, (1) evaluation of disaster preparedness in local communities and health-care facilities, (2) study on risk communication in public health emergencies, (3) epidemiological study on those children with cerebral palsy, and (4) various public health issues due to the pandemic of COVID-19.

References

(Original Article)

1. Tanaka H, Mackenbach JP, Kobayashi Y. Widening socioeconomic inequalities in smoking in Japan, 2001–2016. Journal of Epidemiology 31(6): 369-377, 2021.
2. Maeda E, Ishihara O, Tomio J, Miura H, Kobayashi Y, Terada Y, Murata K, Nomura K. Cesarean delivery rates for overall and multiple pregnancies in Japan: a descriptive study using nationwide health insurance claims data. Journal of Obstetrics and Gynaecology Research 47(6): 2099–2109, 2021.
3. Jwa SC, Ishihara O, Kuwahara A, Saito K, Saito H, Terada Y, Kobayashi Y, Maeda E. Cumulative live birth rate according to the number of receiving governmental subsidies for assisted reproductive technology in Saitama Prefecture, Japan: A retrospective study using individual data for governmental subsidies. Reproductive Medicine and Biology 20: 451-459, 2021.
4. Iba A, Maeda E, Jwa SC, Yanagisawa-Sugita A, Saito K, Kuwahara A, Saito H, Terada Y, Ishihara O, Kobayashi Y. Household income and medical help-seeking for fertility problems among a representative population in Japan. Reproductive Health 18: 165, 2021.
5. Jwa SC, Ishihara O, Kuwahara A, Saito K, Saito H, Terada Y, Kobayashi Y, Maeda E.Social capital and use of assisted reproductive technology in young couples: Ecological study using application information for government subsidies in Japan. SSM Population Health 16: 100995, 2021.
6. Yamana H, Iba A, Tomio J, Ono S, Jo T, Yasunaga H. Treatment of latent tuberculosis infection in patients receiving biologic agents. Journal of Infection and Chemotherapy 27(2): 243-249, 2021.
7. Hara K, Kobayashi Y, Tomio J, Ito Y, Svensson T, Ikesu R, Chung UI, Svensson AK. Claims-based algorithms for common chronic conditions were efficiently constructed using machine learning methods. PLoS One 16(9): e0254394, 2021.
8. Ito Y, Hara K, Sato H, Tomio J. Knowledge, experience, and perceptions of generic drugs among middle-aged adults and their willingness-to-pay: A nationwide online survey in Japan. Tohoku Journal of Experimental Medicine 255(1): 9-17, 2021.
9. Morioka N, Moriwaki M, Tomio J, Fushimi K, Ogata Y. Dementia and patient outcomes after hip surgery in older patients: A retrospective observational study using nationwide administrative data in Japan. PLoS One, 16(4): e0249364, 2021.
10. Abe K, Miyawaki A, Nakamura M, Ninomiya H, Kobayashi Y. Trends in hospitalizations for asthma during the COVID-19 outbreak in Japan. Journal of Allergy and Clinical Immunology: In Practice 9(1): 494–496, 2021.
11. Miyawaki A, Tomio J, Nakamura M, Ninomiya H, Kobayashi Y. Changes in surgeries and therapeutic procedures during the COVID-19 outbreak: A longitudinal study of acute care hospitals in Japan. Annals of Surgery, 273(4): e132–4, 2021.
12. Jin X, Abe K, Taniguchi Y, Watanabe T, Miyawaki A, Tamiya N. Trajectories of long-term care expenditure during the last five years of life in Japan: a nationwide retrospective cohort study. Journal of the American Medical Directors Association 22(11): 2331-2336, 2021
13. Yamamoto A, Gelberg L, Needleman J, Kominski G, Vangala S, Miyawaki A, Tsugawa, Y. Comparison of childbirth delivery outcomes and costs of care between homeless and non-homeless women. JAMA Network Open, 4(4): e217491, 2021.
14. Ikesu R, Miyawaki A, Svensson AK, Svensson T, Kobayashi Y, Chung UI. Association of managerial position with cardiovascular risk factors: A fixed-effects analysis for Japanese employees. Scandinavian Journal of Work, Environment & Health 47(6): 425-434, 2021

15. Sun Y, Iwagami M, Watanabe T, Sakata N, Sugiyama T, Miyawaki A, Tamiya N. Factors for psychological distress in family caregivers: Findings from nationwide data in Japan. Geriatrics Gerontology International 21(9): 855-864, 2021.
16. Gotanda H, Miyawaki A, Tabuchi T, Tsugawa Y. Association between trust in government and practice of preventive measures during the COVID-19 pandemic in Japan. Journal of General Internal Medicine 36(11): 3471-3477, 2021.
17. Sano K, Nakamura M, Ninomiya H, Kobayashi Y, Miyawaki A. Large decrease in paediatric hospitalisations during the COVID-19 outbreak in Japan. BMJ Pediatrics Open, 5(1): e001013, 2021.
18. Ikesu R, Miyawaki A, Sugiyama T, Nakamura M, Ninomiya H, Kobayashi Y. Trends in diabetes care during the COVID-19 outbreak in Japan. Journal of General Internal Medicine, 36(5): 1460-1462, 2021.
19. Miyawaki A, Evans CEL, Lucas PJ, Kobayashi Y. Relationship between social spending and childhood obesity in OECD Countries: an ecological study. BMJ Open, 11(2): e044205, 2021.
20. Miyawaki A. Khullar D, Tsugawa Y. Processes of care and outcomes for homeless patients hospitalised for cardiovascular conditions at safety-net versus non-safety-net hospitals: cross-sectional study. BMJ Open, 11(4): e046959, 2021.
21. Miyawaki A, Tabuchi T, Toyama Y, Tsugawa Y. Association between participation in the government subsidy program for domestic travel and symptoms indicative of COVID-19 infection in Japan: Cross-sectional study. BMJ Open, 11(4): e049069, 2021.
22. Abe K, Kawachi I, Taniguchi Y, Tamiya N. Municipal characteristics of in-home death among care-dependent older Japanese adults. JAMA Network Open, 5(1): e2142273-e2142273, 2021.
23. Abe K, Kawachi I, Watanabe T, Tamiya N. Association of the frequency of in-home care services utilization and the probability of in-home death. JAMA Network Open, 4(11): e2132787-e2132787, 2021.
24. Abe K, Taniguchi Y, Kawachi I, Watanabe T, Tamiya N. Municipal long-term care workforce supply and in-home deaths at the end of life: Panel data analysis with a fixed-effect model in Japan. Geriatrics & Gerontology International 21(8): 712-7, 2021.
25. Taniguchi Y, Iwagami M, Sakata N, Watanabe T, Abe K, Tamiya N. Epidemiology of food choking deaths in Japan: Time trends and regional variations. Journal of Epidemiology 31(5): 356-60, 2021.
26. Miyawaki A, Tabuchi T, Ong MK, Tsugawa Y. Age and social disparities in the use of telemedicine during the COVID-19 pandemic in Japan: Cross-sectional study. Journal of Medical Internet Research 23(7): e27982, 2021.
27. Ichizuka K, Toyokawa S, Ikenoue T, Satoh S, Hasegawa J, Ikeda T, Tamiya N, Nakai A, Fujimori K, Maeda T, Kanayama N, Masuzaki H, Iwashita M, Suzuki H, Takeda S. Risk factors for cerebral palsy in neonates due to placental abruption. Journal of Obstetrics and Gynaecology 47: 159-166, 2021.
28. Tanaka H, Mackenbach JP, Kobayashi Y. Trends and socioeconomic inequalities in self-rated health in Japan, 1986-2016. BMC Public Health 21: 1811, 2021.
29. Kosaka Y, Sugiyama T, Hara K, Kobayashi Y. Adherence to daily, weekly, and monthly dosing regimens of bisphosphonates for osteoporosis treatment in postmenopausal women in Japan: A retrospective study using claims data. Tohoku Journal of Experimental Medicine 255: 147-155, 2021.
30. Yamagishi H, Osaka H, Toyokawa S, Kobayashi Y, Shimoizumi H. Survey on children with cerebral palsy in Tochigi Prefecture, Japan. Pediatrics International 63(8): 951-957, 2021.
31. 田中宏和、小林廉毅. 職業別喫煙率とその推移：国民生活基礎調査による分析（2001-2016年）. 日本公衆衛生雑誌 68 (6): 433-443, 2021.
32. Ihana-Sugiyama N, Sugiyama T, Imai K, Yanagisawa-Sugita A, Tanaka H, Ohsugi M, Ueki K, Tamiya N, Kobayashi Y. Factors associated with the degree of glycemic

deterioration among patients with type 2 diabetes who dropped out of diabetes care: A longitudinal analysis using medical claims and health checkup data in Japan. Journal of Diabetes Investigation 2021 [Epub ahead of print]
33. Moriwaki M, Yuasa H, Kakehashi M, Suzuki H, Kobayashi Y. Impact of social support for mothers as caregivers of cerebral palsy children in Japan. Journal of Pediatric Nursing 2021 [Epub ahead of print]
34. Tanaka H, Mackenbach JP, Kobayashi Y. Estimation of socioeconomic inequalities in mortality in Japan using national census-linked longitudinal mortality data. Journal of Epidemiology 2021 [Epub ahead of print]
35. Inada H, Tomio J, Nakahara S, Ichikawa M. Effect of annual road safety publicity and enforcement campaign on road fatalities in Japan: a time series study from 1949 to 2019. Journal of Epidemiology and Community Health, 2021 [Epub ahead of print]
36. Taniguchi Y, Kuno T, Komiyama J, Adomi M, Suzuki T, Abe T, Ishimaru M, Miyawaki A, Saito M, Ohbe H, Miyamoto Y, Imai S, Kamio T, Tamiya N, Iwagami M. Comparison of patients' characteristics and in-hospital mortality between patients admitted for COVID-19 in 2020 and influenza in 2017-2020: a multicenter, retrospective cohort study in Japan. Lancet Regional Health - Western Pacific, 2021 [Epub ahead of print]
37. Taniguchi Y, Miyawaki A, Tsugawa Y, Murayama H, Tamiya N, Tabuchi T. Family caregiving and changes in mental health status in Japan during the COVID-19 pandemic. Archives of Gerontology and Geriatrics, 2021 [Epub ahead of print]
38. Nakahara S, Inada H, Ichikawa M, Tomio J. Japan's slow response to improve access to inpatient care for COVID-19 patients. Front Public Health, 2021 [Epub ahead of print]
39. Ikesu R, Taguchi A, Hara K, Kawana K, Tsuruga T, Tomio J, Osuga Y. Prognosis of High-Risk Human Papillomavirus-Related Cervical Lesions: A hidden Markov Model analysis of a single-center cohort in Japan. Cancer Medicine, 2021 [Epub ahead of print]
40. Hidaka T, Ogawa K, Tomioka Y, Yoshii K, Tomio J, Okazaki M. Change in eyelid closure in spontaneous blinking after static eyelid reconstruction surgery for patients with facial paralysis. Annals of Plastic Surgery, 2021 [Epub ahead of print]

(Others)

41. 葛西龍樹, 阿部計大, 大浦誠, 加藤大祐, 小林直子, 佐治朝子,豊田喜弘, 原田直樹, 藤谷直樹, 森冬人(翻訳) (原著:Moira Stewart, Judith Belle Brown, W, Wayne Weston, Ian R McWhinney, Carol L McWilliam, Thomas R Freeman). 患者中心の医療の方法 原著第 3 版. 羊土社, 2021. C.
42. Abe K, Kawachi I. Deaths in nursing homes during the COVID-19 pandemic—Lessons from Japan. JAMA Health Forum, 2(2): e210054-e210054, 2021.
43. Abe K, Taniguchi Y, Kawachi I, Watanabe T, Tamiya N. Authors' reply to the letter from Dr. Kato. Geriatrics & Gerontology International, 21: 970, 2021. https://doi.org/10.1111/ggi.14270
44. 阿部計大. COVID-19 流行下の研究留学. DOCTORASE,37, 2021.
45. 小林廉毅. 第 80 回日本公衆衛生学会総会(巻頭言). ビルと環境 175: 3-4, 2021.
46. Miyawaki A, Tsugawa Y. Health and Public Health Implications of COVID-19 in Asian Countries. Asian Economic Policy Review, 17, 18-36, 2021. [Epub ahead of print]
47. Miyawaki A, Tsugawa Y. Why do homeless women in New York state experience fewer hospital revisits after childbirth than housed women? BMJ Quality & Safety, 2021. [Epub ahead of print]
48. 宮脇敦士：「医療ビッグデータから見えてくるもの」読売新聞 (yomiDr.), 2021 年 4 月-2022 年 3 月
49. Kobayahsi Y (as the speaker in Session 1.1.Presentations): Session 1 Regional Focus: Asia and Australia-New Zealand. An International Symposium － Towards the Post-Pandemic Era, Online, June 18-19 and 25, 2021.
50. Miyawaki A (invited speaker, with Dr. Yusuke Tsugawa) Health and Public Health Implications of COVID-19 in Asian Countries. The 33rd

conference of Asian Economic Policy Review (AEPR) conference, Japan Center for Economic Research, Online, April 9-10, 2021.
51. 第 80 回日本公衆衛生学会総会 (学会長: 小林廉毅), 東京, 2021 年 12 月 21-23 日.小林廉毅: 学会長講演「公衆衛生学の基盤：統計と調査」.

Social Medicine

2. Forensic Medicine, and Medical Informatics and Economics

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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 Furuhata 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 finger-printing 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.

Hirotaro 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 120 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.

It should be noted that this year that pandemic of the new coronavirus (SARS-CoV-2) continued. Infection control in dissection has become a hot topic, but with the introduction of the laminar-flow autopsy table following the seismic retrofitting carried out in 2019, it 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, conducting a SARS-CoV-2 PCR test in all cases. Last year, we had several COVID-19 cases, and autopsies were performed with PAPRs (powered air-purifying respirators).

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, DNA typing, histology) or experiments. 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 Hearth 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 have studied lipid oxidation in cases of muscle crush syndrome and methamphetamine intoxication. 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 University of New Mexico Department of pathology and others, we are also studying the characteristics of postmortem CT in COVID-19 deaths.

Publications

1. Nagasawa S, Saka K, Yamagishi Y, Yajima D, Chiba F, Yamaguchi R, Torimitsu S, Iwase H. Association between sexual activity-related death and non-prescription use of phosphodiesterase type 5 inhibitors. Leg Med (Tokyo). 2021; 48: 101815.
2. Nagasawa S, Yamaguchi R, Saka K, Torimitsu S,Chiba F, Yajima D, Inokuchi G, Motomura A, Kira K,Yamagishi Y, Ogra O, Iwase H. Ropinirole involved in a fatal case; blood and urinary concentrations. Forensic Toxicology, 2021; onlone first.
3. Mizuno S, Ono S, Yasunaga H, Iwase H,Factors associated with methamphetamine use in Japanese people who died of unnatural causes: Analysis using forensic autopsy reports, Forensic Sci. Int. 2021; 327: 110946-119453.
4. Kihara Y, Makino Y, Nakajima M, Tsuneya S, Tanaka A, Yamaguchi R, Torimitsu S, Hayama SI, Iwase H. Experimental water injection into lungs using an animal model: Verification of the diatom concentration test to diagnose drowning. Forensic Sci Int. 2021 Oct; 327: 110983.
5. Tsuneya S, Nakajima M, Makino Y, Torimitsu S, Yamaguchi R, Iwase H. A quantitative comparison between using sodium hypochlorite as a digestion method for the diatom test and the conventional method using fuming nitric acid. Forensic Sci Int. 2021 Dec; 329: 111086.
6. Nagasawa S, Mori A, Hirata Y, Motomura A, Ishii N, Okaba K, Horioka K, Makino Y, Nakajima M, Torimitsu S, Yamagushi R, Inokuchi G, Chiba F, Hoshioka Y, Saito N, Yoshida M, Yajima D, Akitomi S, Iwase H, Saitoh H. SmartAmp method can rapidly detect SARS-Cov-2 in dead bodies. Foresic Sci Int 2021; 331:
7. Yoshida M, Makino Y, Hoshioka Y, Saito N, Yamaguchi R, Chiba F, Inokuchi G, Iwase H. Technical and interpretive pitfalls of postmortem CT: Five examples of errors revealed by autopsy. J Forensic Sci. 2022 Jan;67(1):395-403
8. Yamaguchi R, Sakurada K, Saitoh H, Yoshida M, Makino Y, Torimitsu S, Mizuno S, Iwase H. Fatal airway obstruction due to Ludwig's angina from severe odontogenic infection during antipsychotic medication: A case report and a literature review. J Forensic Sci. 2021; 66 (1): 1980-1985.
9. Unuma K, Makino Y, Yamamoto K, Hattori S, Arai N, Sakai K, Kitagawa M, Uemura K, Kanegane H. Fatal intracranial hemorrhage due to infantile acute lymphoblastic leukemia mimicking abusive head trauma. J Forensic Sci. 2021; 66: 2504-2510.
10. Urabe S, Ishihara K, Chiba F, Yamaguchi R, Shiko Y, Kawasaki Y, Iwase H. Children's death survey using death certificates in the Chiba prefecture. Forensic Science International: Reports. 2021; Volume 4, 100246: 1-11.
11. Torimitsu S, Abe H, Makino Y, Yamaguchi R, Motomura A, Hoshioka Y, Iwase H. Streptococcal toxic shock syndrome with fatal outcome: Report on four forensic autopsy cases. Leg Med (Tokyo). 2021; 50: 101851.
12. Tsuneya S, Makino Y, Chiba F, Kojima M, Yoshida M, Kishimoto T, Mukai H, Hattori S, Iwase H. Postmortem magnetic resonance imaging revealed bilateral globi pallidi lesions in a death associated with prolonged carbon monoxide poisoning: a case report. Int J Legal Med. 2021; 135: 921-928.

13. Jackson NR, Zeigler K, Torrez M, Makino Y, Adolphi NL, Lathrop S, Decker L Dvorscak L, Proe L, Paul ID, Zumwalt R, Jarrell H. New Mexico's COVID-19 Experience. Am J Forensic Med Pathol. 2021; 42: 1-8.
14. Norii T, Makino Y, Unuma K, Hatch GM, Adolphi NL, Dallo S, Albright D, Sklar DP, Braude D. Extraglottic Airway Device Misplacement: A Novel Classification System and Findings in Postmortem Computed Tomography. Ann Emerg Med. 2021; 77: 285-295.
15. Norii T, Makino Y, Unuma K, Adolphi NL, Albright D, Sklar DP, Crandall C, Braude D. CT imaging of extraglottic airway device-pictorial review. Emerg Radiol. 2021; 28: 665-673.
16. Kudo K, Saka K, Waters B, Hara K, Matsusue A, Kashiwagi M, Kubo S. Effects of putrefaction on the quantitative analyses of diphenhydramine in blood and tissues: model experiments by the routine matrix-matched calibration method and standard addition method with different internal standards. Forensic Toxicol. 2021; 39: 437-450.

Department of Biomedical Informatics

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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 ot 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 2021, the faculty composition, including the hospital staff, is 1 professor (Ohe), 1 associate professor (Waki), 2 lecturers (Atarashi, Yokota), 1 specially appointed lecturer (Ida), 1 assistant professor (specially appointed lecturer (hospital)). (Doi), 4

assistant professors (Nagae, Mori, Seki, Yamada), and 2 special assistant professors (Miyake, Kubota). In addition to this, 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, I was in charge of one lecture on medical informatics and clinical medical ontology. In this way, 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. Aoki M, Yokota S, Kagawa R, Shinohara E, Imai T, Ohe K. Automatic Coding Classification of Electronic Nursing Narrative Records Based on Japanese Standard Terminology for Nursing. CIN: Computers, Informatics, Nursing. 2021;39(11): 828-834.
2. Ono S, Ishimaru M, Ida Y, Yamana H, Ono Y, Hoshi K, Yasunaga H. Validity of Diagnoses and Procedures in Japanese Dental Claims Data. BMC Health Services Research. 2021;21(1):1116.
3. Kodama T, Ida Y, Oshima K, Miura H. Are Public Oral Care Services Evenly Distributed?-Nation-Wide Assessment of the Provision of Oral Care in Japan Using the National Database of Health Insurance Claims. International Journal of Environmental Research and Public Health. 2021;18(20): 10850.
4. Oshima K, Kodama T, Ida Y, Miura H. Gender Differences in Work Status during Early Career of Dentists: An Analysis of National Survey Cohort Data of 10 Years in Japan. International Journal of Environmental Research and Public Health. 2021; 18(5):2335.
5. Kawazoe Y, Shibata D, Shinohara E, Aramaki E, Ohe K. A clinical specific BERT developed using a huge Japanese clinical text corpus. PLOS ONE. 2021;16(11): e0259763.
6. Kawaki Y, Sankoda A, Waki K, Miyake K, Hayashi A, Mieno M, Wakui H, Tsurutani Y, Saito J, Hirawa N, Yamakawa T, Komiya S, Isogawa A, Satoh S, Minami T, Osada U, Iwamoto T, Takano T, Terauchi Y, Tamura K, Yamauchi T, Kadowaki T, Nangaku M, Kashihara N, Ohe K. Efficacy of the Self-management Support System DialBetesPlus for Diabetic Kidney Disease: Protocol for a Randomized Controlled Trial. JMIR Research Protocols. 2021;10(8):e31061.
7. 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.
8. Ma X, Imai T, Shinohara E, Kasai S, Kato K, Kagawa R, Ohe K. EHR2CCAS: A framework for mapping EHR to disease knowledge presenting causal chain of disorders – chronic kidney disease example. Journal of Biomedical Informatics. 2021; 115: 10369.
9. Yamaguchi R, Kawazoe Y, Shimamoto K, Shinohara E, Tsukamoto T, Shintani-Domoto Y, Nagasu H, Uozaki H, UshikuT, Nangaku M, Kashihara N, Shimizu A, Nagata M, Ohe K. Glomerular Classification Using Convolutional Neural Networks Based on Defined Annotation Criteria and Concordance Evaluation Among Clinicians. Kidney International Reports. 2021; 6(3): 716-726.
10. Seki T, Kawazoe Y, Ohe K. Machine learning-based prediction of in-hospital mortality using admission laboratory data: A retrospective, single-site study using electronic health record data. PLoS ONE. 2021;16(2): e0246640.
11. Susumu Katsushika, Satoshi Kodera, Mitsuhiko Nakamoto, Kota Ninomiya, Shunsuke Inoue, Shinnosuke Sawano, Nobutaka Kakuda, Hiroshi Takiguchi, Hiroki Shinohara, Ryo Matsuoka, Hirotaka Ieki, Yasutomi Higashikuni, Koki Nakanishi, Tomoko Nakao, Tomohisa Seki, Norifumi Takeda, Katsuhito Fujiu, Masao Daimon,

Hiroshi Akazawa, Hiroyuki Morita, Issei Komuro. The Effectiveness of a Deep Learning Model to Detect Left Ventricular Systolic Dysfunction from Electrocardiograms. International Heart Journal 62(6) 1332-1341 2021.11

12. Shinnosuke Sawano, Satoshi Kodera, Susumu Katsushika, Mitsuhiko Nakamoto, Kota Ninomiya, Hiroki Shinohara, Yasutomi Higashikuni, Koki Nakanishi, Tomoko Nakao, Tomohisa Seki, Norifumi Takeda, Katsuhito Fujiu, Masao Daimon, Hiroshi Akazawa, Hiroyuki Morita, Issei Komuro. Deep learning model to detect significant aortic regurgitation using electrocardiography. Journal of Cardiology 2021.9
13. Dai Kusumoto, Tomohisa Seki, Hiromune Sawada, Akira Kunitomi, Toshiomi Katsuki, Mai Kimura, Shogo Ito, Jin Komuro, Hisayuki Hashimoto, Keiichi Fukuda, Shinsuke Yuasa. Anti-senescent drug screening by deep learning-based morphology senescence scoring. Nature communications 12(1) 257-257 2021.1

Internal Medicine

1. Medicine Ⅰ

Department of Cardiovascular Medicine

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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 Ryozo Nagai, the second professor, the present professor Issei Komuro was elected in August, 2012. Our department comprises one professor, 4 lecturers, 2 hospital lecturers, 15 research assistants, 9 staff members, and 44 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 2021, a total of 1,737 patients were newly admitted to our hospital ward of 61 beds. The average duration of hospitalization was 11.0 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 2021, 18 patients underwent heart transplant (total 171 cases). In March 2014, our facility was also authorized to perform lung transplantation. Coronary angiography was performed in 2,049 patients, of which 417 patients underwent percutaneous coronary interventions. CT coronary angiography and cardiovascular MRI were performed in 610 and 158 patients, respectively. With regard to arrhythmias, there were 277 cases of catheter ablation, 149 cases of implantation or replacement of pacemakers and other specialized pacemaker devices, including 25 cases of implantation or replacement of implantable cardioverter-defibrillator and 20 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 178.8 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 (2020)

1. Adachi Y, Kiyosue A, Ando J, Kawahara T, Kodera S, Minatsuki S, Kikuchi H, Inaba T, Kiriyama H, Hirose K, Shinohara H, Saito A, Fujiwara T, Hara H, Ueda K, Sakakura K, Hatano M, Harada M, Takimoto E, Akazawa H, Morita H, Momomura SI, Fujita H and Komuro I. Factors associated with left ventricular reverse remodelling after percutaneous coronary intervention in patients with left ventricular systolic dysfunction. Sci Rep 11:239, 2021.
2. Bujo C, Amiya E, Hatano M, Tsuji M, Maki H, Ishida J, Ishii S, Narita K, Endo M, Ando M, Shimada S, Kinoshita O, Ono M and Komuro I. Association between infectious event and de novo malignancy after heart transplantation. Heart Vessels 36:499-508, 2021.
3. Fujiwara T, Takeda N, Hara H, Ishii S, Numata G, Tokiwa H, Maemura S, Suzuki T, Takiguchi H, Kubota Y, Seo K, Sakata A, Nomura S, Hatano M, Ueda K, Harada M, Toko H, Takimoto E, Akazawa H, Nishimura S and Komuro I. Three-Dimensional Visualization of Hypoxia-Induced Pulmonary Vascular Remodeling in Mice. Circulation 144: 1452-1455, 2021.
4. Hartiala JA, Han Y, Jia Q, Hilser JR, Huang P, Gukasyan J, Schwartzman WS, Cai Z, Biswas S, Tregouet DA, Smith NL, Consortium I, Group CCHW, Consortium G-C, Seldin M, Pan C, Mehrabian M, Lusis AJ, Bazeley P, Sun YV, Liu C, Quyyumi AA, Scholz M, Thiery J, Delgado GE, Kleber ME, Marz W, Howe LJ, Asselbergs FW, van Vugt M, Vlachojannis GJ, Patel RS, Lyytikainen LP, Kahonen M, Lehtimaki T, Nieminen TVM, Kuukasjarvi P, Laurikka JO, Chang X, Heng CK, Jiang R, Kraus WE, Hauser ER, Ferguson JF, Reilly MP, Ito K, Koyama S, Kamatani Y, Komuro I,

Biobank J, Stolze LK, Romanoski CE, Khan MD, Turner AW, Miller CL, Aherrahrou R, Civelek M, Ma L, Bjorkegren JLM, Kumar SR, Tang WHW, Hazen SL and Allayee H. Genome-wide analysis identifies novel susceptibility loci for myocardial infarction. Eur Heart J 42:919-933, 2021.

5. Hirose K, Nakanishi K, Daimon M, Sawada N, Yoshida Y, Ishiwata J, Hirokawa M, Koyama K, Nakao T, Fujiu K, Morita H, Di Tullio MR, Homma S and Komuro I. Correlation Between the Cohorts for Heart and Aging Research in Genomic Epidemiology-Atrial Fibrillation Risk Score and Left Atrial Remodeling in the General Population. Circ Arrhythm Electrophysiol 14:e009826, 2021.
6. Hirose K, Nakanishi K, Daimon M, Sawada N, Yoshida Y, Iwama K, Yamamoto Y, Ishiwata J, Hirokawa M, Koyama K, Nakao T, Morita H, Di Tullio MR, Homma S and Komuro I. Impact of insulin resistance on subclinical left ventricular dysfunction in normal weight and overweight/obese japanese subjects in a general community. Cardiovasc Diabetol 20:22, 2021.
7. Ishiwata J, Daimon M, Nakanishi K, Sugimoto T, Kawata T, Shinozaki T, Nakao T, Hirokawa M, Sawada N, Yoshida Y, Amiya E, Hatano M, Morita H, Yatomi Y and Komuro I. Combined evaluation of right ventricular function using echocardiography in non-ischaemic dilated cardiomyopathy. ESC Heart Fail 8:3947-3956, 2021.
8. Ishizuka M, Harada M, Nomura S, Ko T, Ikeda Y, Guo J, Bujo S, Yanagisawa-Murakami H, Satoh M, Yamada S, Kumagai H, Motozawa Y, Hara H, Fujiwara T, Sato T, Takeda N, Takeda N, Otsu K, Morita H, Toko H and Komuro I. CXCR7 ameliorates myocardial infarction as a beta-arrestin-biased receptor. Sci Rep 11:3426, 2021.
9. Itoh H, Kaneko H, Kiriyama H, Kamon T, Fujiu K, Morita K, Yotsumoto H, Michihata N, Jo T, Takeda N, Morita H, Yasunaga H and Komuro I. Reverse J-shaped relationship between body mass index and in-hospital mortality of patients hospitalized for heart failure in Japan. Heart Vessels 36:383-392, 2021.
10. Itoh H, Kaneko H, Okada A, Yano Y, Morita K, Seki H, Kiriyama H, Kamon T, Fujiu K, Matsuoka S, Nakamura S, Michihata N, Jo T, Takeda N, Morita H, Nishiyama A, Node K, Yasunaga H and Komuro I. Fasting Plasma Glucose and Incident Colorectal Cancer: Analysis of a Nationwide Epidemiological Database. J Clin Endocrinol Metab, 2021.
11. Itoh H, Kaneko H, Okada A, Yano Y, Morita K, Seki H, Kiriyama H, Kamon T, Fujiu K, Matsuoka S, Nakamura S, Michihata N, Jo T, Takeda N, Morita H, Nishiyama A, Node K, Yasunaga H and Komuro I. Fasting Plasma Glucose and Incident Colorectal Cancer: Analysis of a Nationwide Epidemiological Database Fasting Plasma Glucose and Colorectal Cancer. J Clin Endocrinol Metab, 2021.
12. Jimba T, Kaneko H, Yano Y, Itoh H, Yotsumoto H, Seki H, Morita K, Kiriyama H, Kamon T, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Nishiyama A, Node K, Yasunaga H and Komuro I. Relation of the Metabolic Syndrome to Incident Colorectal Cancer in Young Adults Aged 20 to 49 Years. Am J Cardiol 158:132-138, 2021.
13. Kaneko H, Itoh H, Kamiya K, Morita K, Sugimoto T, Konishi M, Kiriyama H, Kamon T, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Yasunaga H and Komuro I. Acute-phase initiation of cardiac rehabilitation and clinical outcomes in hospitalized patients for acute heart failure. Int J Cardiol 340:36-41, 2021.
14. Kaneko H, Itoh H, Kiriyama H, Kamon T, Fujiu K, Morita K, Michihata N, Jo T, Takeda N, Morita H, Yasunaga H and Komuro I. Possible association between eating behaviors and cardiovascular disease in the general population: Analysis of a nationwide epidemiological database. Atherosclerosis 320:79-85, 2021.
15. Kaneko H, Itoh H, Kiriyama H, Kamon T, Fujiu K, Morita K, Michihata N, Jo T, Takeda N, Morita H, Yasunaga H and Komuro I. Fasting plasma glucose and subsequent cardiovascular disease among young adults: Analysis of a nationwide epidemiological database. Atherosclerosis 319:35-41, 2021.
16. Kaneko H, Itoh H, Yotsumoto H, Kiriyama H, Kamon T, Fujiu K, Morita K, Kashiwabara K, Michihata N, Jo T, Morita H, Yasunaga H and Komuro I. Cardiovascular Health Metrics of 87,160

Couples: Analysis of a Nationwide Epidemiological Database. J Atheroscler Thromb 28:535-543, 2021.
17. Kaneko H, Yano Y, Itoh H, Morita K, Kiriyama H, Kamon T, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Nishiyama A, Node K, Bakris G, Miura K, Muntner P, Viera AJ, Oparil S, Lloyd-Jones DM, Yasunaga H and Komuro I. Untreated Hypertension and Subsequent Incidence of Colorectal Cancer: Analysis of a Nationwide Epidemiological Database. J Am Heart Assoc 10:e022479, 2021.
18. Kaneko H, Yano Y, Itoh H, Morita K, Kiriyama H, Kamon T, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Node K, Carey RM, Lima JAC, Oparil S, Yasunaga H and Komuro I. Association of Blood Pressure Classification Using the 2017 American College of Cardiology/American Heart Association Blood Pressure Guideline With Risk of Heart Failure and Atrial Fibrillation. Circulation 143:2244-2253, 2021.
19. Kiriyama H, Kaneko H, Itoh H, Kamon T, Mizuno Y, Fujiu K, Morita H, Yamamichi N and Komuro I. Association between changes in body weight and lipid profile in the general population: a community-based cohort study. Eur Heart J Qual Care Clin Outcomes 7:109-110, 2021.
20. 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, 2021.
21. Matsuoka S, Kaneko H, Yano Y, Itoh H, Fukui A, Morita K, Kiriyama H, Kamon T, Fujiu K, Seki H, Michihata N, Jo T, Takeda N, Morita H, Nakamura S, Yokoo T, Nishiyama A, Node K, Yasunaga H and Komuro I. Association Between Blood Pressure Classification Using the 2017 ACC/AHA Blood Pressure Guideline and Retinal Atherosclerosis. Am J Hypertens 34:1049-1056, 2021.
22. Nakanishi K, Daimon M, Yoshida Y, Sawada N, Hirose K, Iwama K, Yamamoto Y, Ishiwata J, Hirokawa M, Kaneko H, Nakao T, Mizuno Y, Morita H, Di Tullio MR, Homma S and Komuro I. Subclinical Hypothyroidism as an Independent Determinant of Left Atrial Dysfunction in the General Population. J Clin Endocrinol Metab 106: e1859-e1867, 2021.
23. Nakayama A, Morita H, Kawahara T, Itoh H and Komuro I. Association between testosterone and lipid profiles under statin therapy and its clinical impact on the cardiovascular event risk. Heart Vessels 36:1794-1803, 2021.
24. Sakaue S, Kanai M, Tanigawa Y, Karjalainen J, Kurki M, Koshiba S, Narita A, Konuma T, Yamamoto K, Akiyama M, Ishigaki K, Suzuki A, Suzuki K, Obara W, Yamaji K, Takahashi K, Asai S, Takahashi Y, Suzuki T, Shinozaki N, Yamaguchi H, Minami S, Murayama S, Yoshimori K, Nagayama S, Obata D, Higashiyama M, Masumoto A, Koretsune Y, FinnGen, Ito K, Terao C, Yamauchi T, Komuro I, Kadowaki T, Tamiya G, Yamamoto M, Nakamura Y, Kubo M, Murakami Y, Yamamoto K, Kamatani Y, Palotie A, Rivas MA, Daly MJ, Matsuda K and Okada Y. A cross-population atlas of genetic associations for 220 human phenotypes. Nat Genet 53:1415-1424, 2021.
25. Sawada N, Nakanishi K, Daimon M, Hirose K, Yoshida Y, Ishiwata J, Hirokawa M, Koyama K, Nakao T, Morita H, Di Tullio MR, Homma S and Komuro I. Independent effect of visceral fat on left atrial phasic function in the general population. Nutr Metab Cardiovasc Dis 31:3426-3433, 2021.
26. Shinohara K, Ikeda S, Enzan N, Matsushima S, Tohyama T, Funakoshi K, Kishimoto J, Itoh H, Komuro I and Tsutsui H. Efficacy of intensive lipid-lowering therapy with statins stratified by blood pressure levels in patients with type 2 diabetes mellitus and retinopathy: Insight from the EMPATHY study. Hypertens Res 44:1606-1616, 2021.
27. Sugita J, Fujiu K, Nakayama Y, Matsubara T, Matsuda J, Oshima T, Liu Y, Maru Y, Hasumi E, Kojima T, Seno H, Asano K, Ishijima A, Tomii N, Yamazaki M, Kudo F, Sakuma I, Nagai R, Manabe I and Komuro I. Cardiac macrophages prevent sudden death during heart stress. Nat Commun 12:1910, 2021.
28. Takeda N, Inuzuka R, Yagi H, Morita H, Ando M, Yamauchi H, Taniguchi Y, Porto KJ, Kanaya T, Ishiura H, Mitsui J, Tsuji S, Toda T, Ono M and Komuro I. Clinical Impact of Copy Number

Variation on the Genetic Diagnosis of Syndromic Aortopathies. Circ Genom Precis Med 14:e003458, 2021.

29. Yoshida Y, Nakanishi K, Daimon M, Ishiwata J, Sawada N, Hirokawa M, Kaneko H, Nakao T, Mizuno Y, Morita H, Di Tullio MR, Homma S and Komuro I. Sex-specific difference in the association between arterial stiffness and subclinical left ventricular dysfunction. Eur Heart J Cardiovasc Imaging 22:817-823, 2021.
30. Yoshida Y, Nakanishi K, Daimon M, Ishiwata J, Sawada N, Hirokawa M, Kaneko H, Nakao T, Mizuno Y, Morita H, Di Tullio MR, Homma S and Komuro I. Atrioventricular and Ventricular Functional Interdependence in Individuals Without Overt Cardiac Disease. J Am Heart Assoc 10: e021624, 2021.

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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 profesors. 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 2021

1.	Primary lung cancer	488
2.	Abnormal lung shadows	66
3.	Interstitial pneumonia	45
4.	Respiratory infections	29
5.	Non-tuberculous mycobacterial infections	15
6.	Other cancers	12
7.	Pneumothorax	9
8.	COPD	4
9.	Bronchial Asthma	3

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 unavairable 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 dugs
- 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. Amano Y, Kage H, Tanaka G, Sato Y, Tanaka M, Nagase T. Multiple Brain Metastases in a Patient with ROS1 Fusion-Positive Lung Adenocarcinoma as a Disease Flare due to Crizotinib Cessation Caused by Disseminated Aseptic Inflammation from Crizotinib-Associated Renal Cysts: A Case Report. Case Rep Oncol. 2022 Mar 30;15(1):338-344.
2. Ando T, Kage H, Shinozaki-Ushiku A, Tatsuno K, Tsutsumi S, Nagayama K, Nakajima J, Kohsaka S, Miyagawa K, Aburatani H, Mano H, Nagase T. Composite Clonal Analysis Reveals Transition of NSCLC Subtypes Through Accumulation of Gene Mutations: A Case Report. JTO Clin Res Rep. 2022 Jan 10;3(2):100277.
3. Ishii T, Murakami Y, Narita T, Nunokawa H, Miyake K, Nagase T, Yamashita N. Myeloid differentiation protein-2 has a protective role in house dust mite-mediated asthmatic characteristics with the proinflammatory regulation of airway epithelial cells and dendritic cells. Clin Exp Allergy. 2022 Jan;52(1):149-161.
4. Jo T, Michihata N, Yamana H, Morita K, Ishimaru M, Yamauchi Y, Hasegawa W, Urushiyama H, Uda K, Matsui H, Fushimi K, Yasunaga H, Nagase T. Risk of drug-induced interstitial lung disease in hospitalised patients: a nested case-control study. Thorax. 2021 Dec; 76(12):1193-1199.
5. Miyashita N, Enokido T, Horie M, Fukuda K,

Urushiyama H, Strell C, Brunnström H, Micke P, Saito A, Nagase T. TGF-β-mediated epithelial-mesenchymal transition and tumor-promoting effects in CMT64 cells are reflected in the transcriptomic signature of human lung adenocarcinoma. Sci Rep. 2021 Nov 17;11(1): 22380.

6. Sakamoto Y, Yamauchi Y, Jo T, Michihata N, Hasegawa W, Takeshima H, Matsui H, Fushimi K, Yasunaga H, Nagase T. In-hospital mortality associated with community-acquired pneumonia due to methicillin-resistant Staphylococcus aureus: a matched-pair cohort study. BMC Pulm Med. 2021 Nov 3;21(1):345.
7. Tamiya H, Mitani A, Isago H, Ishimori T, Saito M, Jo T, Tanaka G, Yanagimoto S, Nagase T. Measurement of chest wall motion using a motion capture system with the one-pitch phase analysis method. Sci Rep. 2021 Nov 2;11(1): 21497.
8. Ando T, Kage H, Matsumoto Y, Zokumasu K, Nagase T. Lower dose of ethambutol may reduce ocular toxicity without radiological deterioration for Mycobacterium avium complex pulmonary disease. Respir Investig. 2021 Nov;59(6):777-782.
9. Ikushima H, Hiraishi Y, Toriumi K, Ando T, Tamiya H, Ishida J, Amano Y, Kage H, Tanaka G, Nagase T. Multiple cerebral infarctions in ROS1-rearranged lung adenocarcinoma. Respirol Case Rep. 2021 Aug 26;9(9):e0831.
10. Yokoyama A, Sakamoto Y, Jo T, Urushiyama H, Tamiya H, Tanaka G, Matsui H, Fushimi K, Yasunaga H, Nagase T. Pulmonary disease as a risk factor for transfusion-related acute lung injury. ERJ Open Res. 2021 Aug 31;7(3):00039-2021.
11. Tanaka G, Jo T, Tamiya H, Sakamoto Y, Hasegawa W, Matsui H, Fushimi K, Yasunaga H, Nagase T. Factors affecting in-hospital mortality of non-tuberculous mycobacterial pulmonary disease. BMC Infect Dis. 2021 Jul 20;21(1):698.
12. Watanabe K, Suzukawa M, Arakawa S, Kobayashi K, Igarashi S, Tashimo H, Nagai H, Tohma S, Nagase T, Ohta K. Corrigendum to "Leptin enhances cytokine/chemokine production by normal lung fibroblasts by binding to leptin receptor" [Allergol Int 68S (2019) S3-S8]. Allergol Int. 2021 Jul;70(3):404.
13. Amano Y, Kage H, Tanaka G, Gonoi W, Nakai Y, Kurokawa R, Inui S, Okamoto K, Harada S, Iwabu M, Morizaki Y, Abe O, Moriya K, Nagase T. Diagnostic prediction of COVID-19 based on clinical and radiological findings in a relatively low COVID-19 prevalence area. Respir Investig. 2021 Jul;59(4):446-453.
14. Urushiyama H, Jo T, Hasegawa W, Ando T, Sakamoto Y, Uda K, Matsui H, Fushimi K, Yasunaga H, Nagase T. Preoperative use of pirfenidone and reduced risk of postoperative severe respiratory complications in patients with idiopathic pulmonary fibrosis: Propensity score-matched analysis using a nationwide database in Japan. Respirology. 2021 Jun;26(6): 590-596.
15. Isago H, Mitani A, Kohno S, Nagoshi S, Ishimori T, Saito M, Tamiya H, Miyashita N, Ishii T, Matsuzaki H, Yatomi Y, Nagase T, Jo T. The Japanese Herbal (Kampo) Medicine Hochuekkito Attenuates Lung Inflammation in Lung Emphysema. Biol Pharm Bull. 2021;44(1):39-45.
16. Watanabe K, Suzukawa M, Narumoto O, Kawashima M, Suzuki J, Matsui H, Nagai H, Kurashima A, Nagase T, Tohma S. CD64 expression on neutrophils reflects the activity of nontuberculous mycobacterial lung disease. Respir Investig. 2021 Jan;59(1):155-156.
17. Fukuda K, Matsuzaki H, Mikami Y, Makita K, Miyakawa K, Miyashita N, Hosoki K, Ishii T, Noguchi S, Urushiyama H, Horie M, Mitani A, Yamauchi Y, Shimura E, Nakae S, Saito A, Nagase T, Hiraishi Y. A mouse model of asthma-chronic obstructive pulmonary disease overlap induced by intratracheal papain. Allergy. 2021 Jan;76(1):390-394.

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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, three lecturers, 21 assistant professors, 14 fellows, 62 graduates, and other visiting researchers including students from abroad as of February 2022. 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. Mitsuhiro Fujishiro succeeded Kazuhiko Koike as professor in July 2021.

Clinical activities

The Department of Gastroenterology owns 85 inpatient beds in charge. By using these beds, we saw total 26,779 inpatients with 2,597 new inpatients in an

average hospital stay of 9.3 days in the fiscal year of 2021. 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 61,999 outpatients with 1,710 new outpatients (2.8%) in the fiscal year of 2021. Specialty and subspecialty clinical conferences are held on Monday evening.

The number of treatments for hepatocellular carcinoma, represented by percutaneous radio-frequency ablation, nearly 230 cases per year, is showing one of the greatest achievements in the field. The number of cases undergoing radiofrequency ablation for metastatic liver tumors is also increasing recent years. In addition, we are making efforts to develop an innovation for daily clinical activities. For example, fibrosis progression in chronic liver disease is conventionally assessed by liver biopsy. Recently we can evaluate the stage of liver fibrosis by FibroScan®, newly developed equipment that measures liver stiffness by ultrasound, which is useful for evaluating increasing non-alcoholic steatohepatitis patients. In addition, nearly 100% cure for HCV hepatitis can be achieved by using oral antiviral agents instead of IFN therapy. This will be especially beneficial for elderly patients and advanced fibrotic patients.

ERCP, the standard endoscopic treatment for biliary and pancreatic diseases, is annually performed in about 1,000 cases. Various endoscopic treatments such as endoscopic treatment of bile duct stones in over 1,400 cases and biliary drainage with metal stents for malignant biliary strictures in over 1,000 cases have been performed. We have reported the development and clinical studies of papillary balloon dilation (EPBD) and papillary large balloon dilation (EPLBD) for the treatment of bile duct stones, and many studies on covered metal stents for malignant as well as benign biliary strictures. We have a lot of experience in providing advanced endoscopic treatment for patients who are difficult to receive standard treatment, such as ERCP using a balloon endoscope and transluminal drainage and stone therapy using endoscopic ultrasonography (EUS) for surgically altered anatomy cases. We also perform endoscopic treatment of chronic pancreatitis and pancreatic stone disease. We also provide preoperative chemotherapy for resectable pancreatic cancer and novel chemotherapy for unresectable pancreatic and biliary tract cancer as an advanced medical treatment. We also perform cancer multi-gene panel testing using tumor specimens collected by EUS-FNA. The number of cases of primary sclerosing cholangitis and IgG4-related diseases, which are intractable, is one of the highest in Japan, and we provide medical care to clarify the pathogenesis of these diseases.

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 depart-ments 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 100 cases in 2021). 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 inhibiter.

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 ultrasonography, gastroduodenal endoscopy, and colonoscopy is 12,500 patients, 12,000 patients, and 6,000 patients per year, respectively. In the endoscopy examinations, we diagnose approximately 350 cases of esophageal cancer, 750 cases of gastric cancer, and 2000 cases of colorectal tumor annually, and half of them are treated endoscopically. 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. In addition, recently, we have adopted the hybrid-type clinical practice with the online lecture.

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. Currently, 62 students are in our department.

Research activities

Both basic and clinical researchers are equally encouraged on the condition that the results may eventually contribute to the cure of gastro-enterological 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, patho-genesis 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, organoids, or liquid biopsy, we perform various experiments to translate the basic results into clinics eventually.

Various clinical activities are recorded in data¬base and analyzed. Studies oriented toward evidence-based medicine are highly appreciated. Recent studies include radiofrequency ablation for liver metastasis of colorectal cancer, the impact of metabolic factors in hepatocarcinogenesis. 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.

Selected References

1. Tsuji Y, Ushiku T, Shinozaki T, Yamashita H, Seto Y, Fukayama M, Fujishiro M, Oda I, Katai H, Taniguchi H, Hasatani K, Kaizaki Y, Oga A,

Nishikawa J, Akasaka R, Endo M, Sugai T, Matsumoto T, Koike K. Risk for lymph node metastasis in Epstein-Barr virus-associated gastric carcinoma with submucosal invasion. Dig Endosc. 2021;33(4):592-7.

2. Kato H, Tateishi K, Fujiwara H, Nakatsuka T, Yamamoto K, Kudo Y, Hayakawa Y, Nakagawa H, Tanaka Y, Ijichi H, Otsuka M, Iwadate D, Oyama H, Kanai S, Noguchi K, Suzuki T, Sato T, Hakuta R, Ishigaki K, Saito K, Saito T, Takahara N, Kishikawa T, Hamada T, Takahashi R, Miyabayashi K, Mizuno S, Kogure H, Nakai Y, Hirata Y, Toyoda A, Ichikawa K, Qu W, Morishita S, Arita J, Tanaka M, Ushiku T, Hasegawa K, Fujishiro M, Koike K. MNX1-HNF1B Axis Is Indispensable for Intraductal Papillary Mucinous Neoplasm Lineages. Gastro¬en¬ter-ol¬ogy. 2022;162(4):1272-87.
3. Aoki T, Yamada A, Kato Y, Saito H, Tsuboi A, Nakada A, Niikura R, Fujishiro M, Oka S, Ishihara S, Matsuda T, Nakahori M, Tanaka S, Koike K, Tada T. Automatic detection of various abnormalities in capsule endoscopy videos by a deep learning-based system: a multicenter study. Gastrointest Endosc. 2021;93(1):165-73.
4. Hatta W, Tsuji Y, Yoshio T, Kakushima N, Hoteya S, Doyama H, Nagami Y, Hikichi T, Kobayashi M, Morita Y, Sumiyoshi T, Iguchi M, Tomida H, Inoue T, Koike 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, Kuribasyashi S, Kiyotoki S, Mabe K, Nakamura T, Nakaya N, Fujishiro M, Masamune A. Prediction model of bleeding after endoscopic sub¬mucosal dissection for early gastric cancer: BEST-J score. Gut. 2021;70(3): 476-84.
5. Fujishiro M, Matsumoto T. History of endoscopes: Contribution of the Japan Gastroenterological Endoscopy Society. Dig Endosc. 2022;34 Suppl 2:13-4.
6. Hamada T, Oyama H, Nakai Y, Tada M, Koh H, Tateishi K, Arita J, Hakuta R, Ijichi H, Ishigaki K, Kawaguchi Y, Kogure H, Mizuno S, Morikawa T, Saito K, Saito T, Sato T, Takagi K, Takahara N, Takahashi R, Tanaka A, Tanaka M, Ushiku T, Hasegawa K, Koike K. ABO Blood Group and Risk of Pancreatic Carcinogenesis in Intraductal Papillary Mucinous Neoplasms. Cancer Epidemiol Biomarkers Prev. 2021;30(5):1020-8.
7. Hayata Y, Nakagawa H, Kurosaki S, Kawamura S, Matsushita Y, Hayakawa Y, Suzuki N, Hata M, Tsuboi M, Kinoshita H, Miyabayashi K, Mizutani H, Nakagomi R, Ikenoue T, Hirata Y, Arita J, Hasegawa K, Tateishi K, Koike K. Axin2+ Peribiliary Glands in the Periampullary Region Generate Biliary Epithelial Stem Cells That Give Rise to Ampullary Carcinoma. Gastroenterology. 2021;160(6):2133-48.
8. Sano M, Takahashi R, Ijichi H, Ishigaki K, Yamada T, Miyabayashi K, Kimura G, Mizuno S, Kato H, Fujiwara H, Nakatsuka T, Tanaka Y, Kim J, Masugi Y, Morishita Y, Tanaka M, Ushiku T, Nakai Y, Tateishi K, Ishii Y, Isayama H, Moses HL, Koike K. Blocking VCAM-1 inhibits pancreatic tumour progression and cancer-associated thrombosis/thromboembolism. Gut. 2021;70(9):1713-23.
9. Kishikawa T, Higuchi H, Wang L, Panch N, Maymi V, Best S, Lee S, Notoya G, Toker A, Matesic LE, Wulf GM, Wei W, Otsuka M, Koike K, Clohessy JG, Lee YR, Pandolfi PP. WWP1 inactivation enhances efficacy of PI3K inhibitors while suppressing their toxicities in breast cancer models. J Clin Invest. 2021;131(24):e140436.
10. Tateishi R, Matsumura T, Okanoue T, Shima T, Uchino K, Fujiwara N, Senokuchi T, Kon K, Sasako T, Taniai M, Kawaguchi T, Inoue H, Watada H, Kubota N, Shimano H, Kaneko S, Hashimoto E, Watanabe S, Shiota G, Ueki K, Kashiwabara K, Matsuyama Y, Tanaka H, Kasuga M, Araki E, Koike K; LUCID study investigators. Hepatocellular carcinoma development in diabetic patients: a nationwide survey in Japan. J Gastroenterol. 2021;56(3):261-73.
11. Hangai S, Kawamura T, Kimura Y, Chang CY, Hibino S, Yamamoto D, Nakai Y, Tateishi R, Oshima M, Oshima H, Kodama T, Moriya K, Koike K, Yanai H, Taniguchi T. Orchestration of myeloid-derived suppres¬sor cells in the tumor microenvironment by ubiquitous cellular protein TCTP released by tumor cells. Nat Immunol. 2021;22(8):947-57.

Internal Medicine

2. Medicine Ⅱ

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Introduction and Organization

The Department of Nephrology and Endocrinology is one of the major divisions in the Department of Internal Medicine of the University of Tokyo, which covers nephrology, hypertension, and endocrinology, and also renal diseases associated with diabetes mellitus, cardiovascular diseases, collagen diseases and so on. Usually we have up to 25 inpatients in the hospital. The Professor and each member of the staff have an active responsibility for all clinical activities. Each member has an office and a research laboratory. In our department, almost all members support the clinical works of our residents. We are intimately working together in all clinical activities under the supervision of the professor, the associate professors, and the lecturers.

Clinical activities

The residents are in charge of up to 25 patients of our department and supervised by associates and faculty staffs. We have clinical conferences to discuss the diagnosis and treatment of our patients with all members of the staff. Particularly difficult cases are further discussed with guest specialists from outside.

Nephritis should be morphologically diagnosed by renal biopsy and the optimal treatment should be chosen for each patient. In our department, renal biopsy is actively performed to give the real benefits of treatment to the patients. We also treat diabetic patients with proteinuria and end-stage renal failure. Each staff of our department also works at the hemodialysis unit, thus we can manage patients in every stage of renal diseases. In collaboration with

Department of Urology, we are conducting renal transplantation and promoting peritoneal dialysis.

In the endocrine unit there is a variety of patients having disorders in thyroid, parathyroid, pituitary, adrenal and gonadal glands. It is also our specialty to diagnose and treat secondary hypertension caused by primary aldosteronism, Cushing's syndrome, pheochromocytoma, renal artery stenosis and so on. We often have consultation from other departments concerning disorders of water and mineral metabolism.

Education

We have responsibility for educating undergraduates, graduate students and residents. Our staffs take part in several lectures for undergraduate and graduate students. In addition, our members are actively involved in clinical clerkship for undergraduate students, and other clinical practice. Particularly, we have put emphasis on participation of the students in clinical practice including medical investigations, diagnosis, and treatment. In the wards, we are also educating residents during daily clinical works and periodical lectures concerning kidney and endocrine diseases. Our department also participates in Metabolism Research Course for educating young clinical researchers and fellows in collaboration with Department of Diabetes and Metabolic Diseases, Department of Cardiology, and Department of Geriatric Medicine.

Research

In our department there are more than 30 students of the graduate school. We have research conferences to discuss the results of the research with the Professor and faculty members. As you see in the references below, our research topics are various and cover every field of nephrology, hypertension and endocrinology. We are also actively collaborating with scientists outside the department and outside the University including foreign countries. Achievements of our researches are published in the world's leading journals of nephrology, hypertension and endocrinology.

1. Investigation of mechanism and development of treatment of chronic kidney diseases: from the viewpoints of hypoxia, oxidative stress, epigenetics, carbonyl stress and endoplasmic reticulum stress.
2. Investigation of causes of atypical hemolytic-uremic syndrome.
3. Roles of renal proximal tubule transport in the regulation of plasma volume and blood pressure.
4. Physiological and pathological significance of Na-HCO_3 cotransporter NBCe1.
5. Molecular mechanism of G protein-coupled receptor (GPCR)-mediated signal transduction, and development of a new drug and strategy targeting GPCR.
6. Investigation on pathogenesis of disorders and treatments of mineral and bone metabolism

Department of Hemodialysis & Apheresis

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.

This new Center for Hemodialysis 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 can be monitored seamlessly under the cloud system of our hospital. 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 renal disease (ESRD).
2. Regular hemodialysis therapy for hospitalized ESRD patients. Please note that our center does

not accept holiday dialysis.
3. Emergency hemodialysis and hemodiafiltration for ICU patients.
4. Plasma exchange for neurodegenerative diseases, SLE, TTP, TMA, and pre/post-liver transplant patients.
5. DFPP for collagenous diseases, MG, HCV, and dermatological disorders.
6. LDL apheresis for nephrotic syndrome and ASO patients.
7. White blood cell elimination therapy for ulcerative colitis and rheumatological arthritis.
8. Cell-free and concentrated ascites reinfusion therapy (CART) for refractory ascites.
9. Induction and maintenance of peritoneal dialysis for ESRD.

Education

1. A systematic review course for M2 students, which covers clinical features, diagnosis, and evidence-based therapeutic strategies for acute and chronic renal failure including diabetic nephropathy.
2. Technical development course for medical engineers and nurses.
3. Tutorial course for clinical fellows applying to the speciality of blood purification therapy.
4. Exposure in hemodialysis & apheresis course to second year residents on request.
5. Our state-of-the-art blood purification protocols are summarized in Japanese handbook in 2010 [Apheresis Pocket Manual] and 2011 [CRRT Pocket Manual]. “Apheresis Pocket Manual” has been translated into Chinese and English, and those translated versions have helped a number of non-Japanese-speaking people to learn how to perform apheresis.
6. Our department takes main part in Critical Care Nephrology Course for educating young clinical researchers and fellows in collaboration with Department of Critical Care Medicine.

Research

1. Prognostic analysis for post-liver transplant patients who received plasma exchange therapy.
2. Development and application of a non-invasive pulse hemoglobin meter.
3. Genome wide association study for Nephrotic syndrome and those functional analyses.
4. Association between factors at the initiation of renal replacement therapy and prognosis.
5. Elucidation of basic mechanisms in cardio-renal syndrome and intervention.
6. Pathophysiology of acute kidney injury and its applicability for renal regenerative study.
7. AKI biomarkers and their clinical significance in ICU/CCU.
8. Renal biomarker to determine clinical action ability in CKD and type-2 DN.

Publications

(1) Sugawara Y, Iwagami M, Yoshida Y, Kikuchi K, Ando R, Shinoda T, Ryuzaki M, Nakamoto H, Sakai K, Hanafusa N, Kashihara N, Nangaku M; COVID-19 Task Force Committee of the Japanese Association of Dialysis Physicians; Japanese Society for Dialysis Therapy; and the Japanese Society of Nephrology. Nationwide survey of the coronavirus disease 2019 prevention and treatment systems for kidney disease patients: a study of Japanese Society of Nephrology-certified educational facilities. Clin Exp Nephrol. 2021 Sep;25(9):996-1002.

(2) Hasegawa S, Okada A, Aso S, Kumazawa R, Matsui H, Fushimi K, Yasunaga H, Nangaku M. Association Between Diabetes and Major Bleeding Complications of Renal Biopsy. Kidney Int Rep. 2021 Nov 25;7(2):232-240.

(3) Kurata Y, Tanaka T, Cernecka H, Eitner F, Nangaku M. TRPM2 Plays a Minor Role in AKI and Kidney Fibrosis. Kidney360. 2021 Oct 22; 3(1):153-157.

(4) Hidaka N, Kato H, Koga M, Katsura M, Oyama Y, Kinoshita Y, Fukumoto S, Makita N, Nangaku M, Ito N. Induction of FGF23-related hypophosphatemic osteomalacia by alcohol consumption. Bone Rep. 2021 Oct 16;15:101144.

(5) Kotani A, Oda Y, Hirakawa Y, Nakamura M, Hamasaki Y, Nangaku M. Peritoneal Dialysis-Related Peritonitis Caused by Streptococcus oralis. Intern Med. 2021 Nov 1;60(21):3447-3452.

(6) Kato H, Hidaka N, Koga M, Kinoshita Y, Nangaku M, Makita N, Ito N. Altered Thyroid

Function Tests Observed in Hypophosphatasia Patients Treated with Asfotase Alfa. Int J Endocrinol. 2021 Oct 28;2021:5492267.

(7) Nangaku M, Kondo K, Takabe S, Ueta K, Kaneko G, Otsuka M, Kawaguchi Y, Komatsu Y. Vadadustat for anemia in chronic kidney disease patients on peritoneal dialysis: A phase 3 open-label study in Japan. Ther Apher Dial. 2021 Oct;25(5):642-653.

(8) Fujii R, Hasegawa S, Maekawa H, Inoue T, Yoshioka K, Uni R, Ikeda Y, Nangaku M, Inagi R. Decreased IFT88 expression with primary cilia shortening causes mitochondrial dysfunction in cisplatin-induced tubular injury. Am J Physiol Renal Physiol. 2021 Sep 1;321(3):F278-F292.

(9) Kurakawa KI, Okada A, Manaka K, Konishi T, Jo T, Ono S, Uda K, Michihata N, Matsui H, Fushimi K, Yamaguchi S, Yamauchi T, Nangaku M, Yasunaga H, Kadowaki T. Clinical Characteristics and Incidences of Benign and Malignant Insulinoma Using a National Inpatient Database in Japan. J Clin Endocrinol Metab. 2021 Nov 19;106(12):3477-3486.

(10) Nangaku M, Kondo K, Ueta K, Kokado Y, Kaneko G, Matsuda H, Kawaguchi Y, Komatsu Y. Efficacy and safety of vadadustat compared with darbepoetin alfa in Japanese anemic patients on hemodialysis: a Phase 3, multicenter, randomized, double-blind study. Nephrol Dial Transplant. 2021 Aug 27;36(9):1731-1741.

(11) Kato H, Koga M, Kinoshita Y, Taniguchi Y, Kobayashi H, Fukumoto S, Nangaku M, Makita N, Ito N. Incidence of Complications in 25 Adult Patients With X-linked Hypophosphatemia. J Clin Endocrinol Metab. 2021 Aug 18;106(9): e3682-e3692.

(12) Fukui K, Tanaka T, Nangaku M. Enarodustat to treat anemia in chronic kidney disease. Drugs Today (Barc). 2021 Aug;57(8):491-497.

(13) 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.

(14) Akizawa T, Nangaku M, Yamaguchi T, Koretomo R, Maeda K, Miyazawa Y, Hirakata H. A Phase 3 Study of Enarodustat in Anemic Patients with CKD not Requiring Dialysis: The SYMPHONY ND Study. Kidney Int Rep. 2021 May 12;6(7):1840-1849.

(15) Manaka K, Sato J, Takeuchi M, Watanabe K, Kage H, Kawai T, Sato Y, Miyagawa T, Yamada D, Kume H, Sato S, Nagase T, Iiri T, Nangaku M, Makita N. Immune checkpoint inhibitor combination therapies very frequently induce secondary adrenal insufficiency. Sci Rep. 2021 Jun 2;11(1):11617.

(16) Sugahara M, Pak WLW, Tanaka T, Tang SCW, Nangaku M. Update on diagnosis, patho-physiology, and management of diabetic kidney disease. Nephrology (Carlton). 2021 Jun;26(6): 491-500.

(17) Nakai K, Tsurutani Y, Inoue K, Matsui S, Makita K, Yamazaki Y, Sasano H, Makita N, Nangaku M, Saito J, Omura M, Nishikawa T. Steroidogenic Activity in Unresected Adrenals Associated With Surgical Outcomes in Primary Aldosteronism. Hypertension. 2021 May 5;77(5): 1638-1646.

(18) Higashihara T, Nishi H, Takemura K, Watanabe H, Maruyama T, Inagi R, Tanaka T, Nangaku M. β2-adrenergic receptor agonist counteracts skeletal muscle atrophy and oxidative stress in uremic mice. Sci Rep. 2021 Apr 28;11(1):9130.

(19) Nangaku M, Kondo K, Kokado Y, Ueta K, Kaneko G, Tandai T, Kawaguchi Y, Komatsu Y. Phase 3 Randomized Study Comparing Vadadustat with Darbepoetin Alfa for Anemia in Japanese Patients with Nondialysis-Dependent CKD. J Am Soc Nephrol. 2021 Apr 21;32(7): 1779–90.

(20) Hasegawa S, Inoue T, Nakamura Y, Fukaya D, Uni R, Wu CH, Fujii R, Peerapanyasut W, Taguchi A, Kohro T, Yamada S, Katagiri M, Ko T, Nomura S, Nakanishi Ozeki A, Susaki EA, Ueda HR, Akimitsu N, Wada Y, Komuro I, Nangaku M, Inagi R. Activation of Sympathetic Signaling in Macrophages Blocks Systemic Inflammation and Protects against Renal Ischemia-Reperfusion Injury. J Am Soc Nephrol. 2021 Apr 19;32(7):1599–615.

(21) 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.

(22) Nangaku M, Kadowaki T, Yotsuyanagi H, Ohmagari N, Egi M, Sasaki J, Sakamoto T, Hasegawa Y, Ogura T, Chiba S, Node K, Suzuki R, Yamaguchi Y, Murashima A, Ikeda N, Morishita E, Yuzawa K, Moriuchi H, Hayakawa S, Nishi D, Irisawa A, Miyamoto T, Suzuki H, Sone H, Fujino Y. The Japanese Medical Science Federation COVID-19 Expert Opinion English Version. JMA J. 2021 Apr 15;4(2):148-162.

(23) 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.

(24) Nangaku M, Yoshino K, Oda Y, Kimura M, Kimura H, Hirose Y, Shirayama Y, Iyo M. Astroglial glutamate transporter 1 and glutamine synthetase of the nucleus accumbens are involved in the antidepressant-like effects of allopregnanolone in learned helplessness rats. Behav Brain Res. 2021 Mar 5;401:113092. doi:

(25) 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.

(26) Sugawara Y, Iwagami M, Kikuchi K, Yoshida Y, Ando R, Shinoda T, Ryuzaki M, Nakamoto H, Sakai K, Hanafusa N, Kashihara N, Nangaku M; COVID-19 Task Force Committee of the Japanese Association of Dialysis Physicians, the Japanese Society for Dialysis Therapy, and the Japanese Society of Nephrology. Infection prevention measures for patients undergoing hemodialysis during the COVID-19 pandemic in Japan: a nationwide questionnaire survey. Ren Replace Ther. 2021;7(1):27.

(27) Inoue D, Nishi H, Inoue R, Nangaku M. Regional Distribution of Cardiologists and Prescription Patterns of Sodium-Glucose Transporter-2 Inhibitors in Japan. Int Heart J. 2021;62(3): 592-600.

(28) Nangaku M, Hamano T, Akizawa T, Tsubakihara Y, Nagai R, Okuda N, Kurata K, Nagakubo T, Jones NP, Endo Y, Cobitz AR. Daprodustat Compared with Epoetin Beta Pegol for Anemia in Japanese Patients Not on Dialysis: A 52-Week Randomized Open-Label Phase 3 Trial. Am J Nephrol. 2021;52(1):26-35.

(29) Yamazaki T, Mimura I, Tanaka T, Nangaku M. Treatment of Diabetic Kidney Disease: Current and Future. Diabetes Metab J. 2021 Jan;45(1): 11-26.

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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 3 former departments 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 (Associate Professor: Dr. Makoto Kurano), 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; annual evaluation of the teaching skill by the students always rates our department within the three places of the top. In addition, there are 12 students of Graduate School in our division. With all these 52 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 293 new patients this year (total 34,764 patients per year). On the inpatient ward, we not only take care of around 24 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 every weekday in the inpatient ward, and also give lectures twice a week in the outpatient unit. In addition, in collaboration with ancillary staffs of our hospital, we provide patients well-reasoned instructions regarding nutritional management, excise therapy and medical therapy.

The weekly official activities of our department consist of the pre-round case conference and the Ward Round by the Professor 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, and Ophthalmology.

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 provide advanced teaching through the seminars and grand conference.

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 β cell proliferation and inter-tissue communication of glucose metabolism in obesity disease and type 2 diabetes. Recently, we are investigating brown and white adipocyte-specific transcriptional and epigenetic regulations in obesity. 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, hyperlipidemia 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. We investigated anti-aging effect of Nicotinamide mononucleotide on muscle function, association between tear and blood glucose concentrations and investigator initiated clinical trials targeting for a new class of anti-diabetic agents.

References

1. Aihara M, Kubota N, Minami T, Shirakawa R, Sakurai Y, Hayashi T, Iwamoto M, Takamoto I, Kubota T, Suzuki R, Usami S, Jinnouchi H, Aihara M, Yamauchi T, Sakata T, Kadowaki T.: Association between tear and blood glucose concentrations: Random intercept model adjusted with confounders in tear samples negative for occult blood. J Diabetes Investig. 12(2):266-276, 2021
2. Alfadda AA, Caterson ID, Coutinho W, Cuevas A, Dicker D, Halford JCG, Hughes CA, Iwabu M, Kang JH, Nawar R, Reynoso R, Rhee N, Rigas G, Salvador J, Vázquez-Velázquez V, Sbraccia P.: The 3Ds - Discussion, diagnosis and direction: Elements for effective obesity care by healthcare professionals. Eur.J.Intern.Med. pii:S0953-6205(21)00012-1, 2021
3. Amano Y, Kage H, Tanaka G, Gonoi W, Nakai Y, Kurokawa R, Inui S, Okamoto K, Harada S, Iwabu M, Morizaki Y, Abe O, Moriya K, Nagase T.: Diagnostic prediction of COVID-19 based on clinical and radiological findings in a relatively low COVID-19 prevalence area. Respir.invest. pii: S2212-5345(21)00045-9, 2021
4. Dicker D, Alfadda AA, Coutinho W, Cuevas A, Halford JCG, Hughes CA, Iwabu M, Kang JH, Nawar R, Reynoso R, Rhee N, Rigas G, Salvador J, Sbraccia P, Vázquez-Velázquez V, Caterson

ID. : Patient motivation to lose weight: Importance of healthcare professional support, goals and self-efficacy. Eur.J.Intern.Med. pii: S0953-6205(21)00019-4, 2021

5. Furuzono S, Kubota T, Taura J, Konishi M, Naito A, Tsutsui M, Karasawa H*, Kubota N*, Kadowaki T* A xanthene derivative, DS20060511, attenuates glucose intolerance by inducing skeletal muscle-specific GLUT4 translocation in mice. *Commun. Biol.* 4:994, 2021. (*co-corresponding authors).
6. Hasegawa Y, Ijichi H*, Saito K, Ishigaki K, Takami M, Sekine R, Usami S, Nakai Y, Koike K, Kubota N*. Protein intake after the initiation of chemotherapy is an independent prognostic factor for overall survival in patients with unresectable pancreatic cancer: A prospective cohort study. *Clin. Nutr.* 40:4792-4798, 2021. (*co-corresponding authors).
7. Hayashi T, Kubota T, Inoue M, Takamoto I, Aihara M, Sakurai Y, Wada N, Miki T, Yamauchi T, Kubota N*, Kadowaki T*. Lack of brain insulin receptor substrate-1 causes growth retardation, with decreased expression of growth hormone-releasing hormone in the hypothalamus. *Diabetes* 70: 1640-1653, 2021. (*co-corresponding authors)
8. Hamaguchi Y, Noma H, Nagashima K, Yamada T, Furukawa TA. : Frequentist performances of Bayesian prediction intervals for random-effects meta-analysis. Biom J. 2021 Feb;63(2):394-405.
9. Hosoe J, Kawashima-Sonoyama Y, Miya F, Kadowaki H, Suzuki K, Kato T, Matsuzawa F, Aikawa SI, Okada Y, Tsunoda T, Hanaki K, Kanzaki S, Shojima N, Yamauchi T, Kadowaki T. Kawai Y, Sankoda A, Genotype-Structure-Phenotype Correlations of Disease-Associated IGF1R Variants and Similarities to Those of INSR Variants. Diabetes. 70:1874-1884, 2021
10. Hosoe J, Suzuki K, Miya F, Kato T, Tsunoda T, Okada Y, Horikoshi M, Shojima N, Yamauchi T, Kadowaki T. Structural basis of ethnic-specific variants of PAX4 associated with type 2 diabetes. Hum Genome Var. 8: 25, 2021
11. Imamura M, Takahashi A, Matsunami M, Horikoshi M, Iwata M, Araki SI, Toyoda M, Susarla G, Ahn J, Park KH, Kong J, Moon S, Sobrin L, Yamauchi T, Tobe K, Maegawa H, Kadowaki T, Maeda S. Genome-Wide Association Studies Identify Two Novel Loci Conferring Susceptibility to Diabetic Retinopathy in Japanese Patients with Type 2 Diabetes. Hum Mol Genet. 30:716-726, 2021
12. Ishihama S, Yoshida S, Yoshida T, Mori Y, Ouchi N, Eguchi S, Sakaguchi T, Tsuda T, Kato K, Shimizu Y, Ohashi K, Okumura T, Bando YK, Yagyu H, Wettschureck N, Kubota N, Offermanns S, Kadowaki T, Murohara T, Takefuji M. LPL/AQP7/GPD2 promotes glycerol metabolism under hypoxia and prevents cardiac dysfunction during ischemia. *FASEB J.* 35: e22048, 2021
13. Iso H, Cui R, Takamoto I, Kiyama M, Saito I, Okamura T, Miyamoto Y, Higashiyama A, Kiyohara Y, Ninomiya T, Yamada M, Nakagawa H, Sakurai M, Shimabukuro M, Higa M, Shimamoto K, Saito S, Daimon M, Kayama T, Noda M, Ito S, Yokote K, Ito C, Nakao K, Yamauchi T, Kadowaki T. Risk Classification for Metabolic Syndrome and the incidence of Cardiovascular Disease in Japan with the Low Prevalence of Obesity: A Pooled Analysis for 10 Prospective Cohort Studies. J Am Heart Assoc.10:23 e 020760, 2021
14. Iwabu M, Okada-Iwabu M, Tanabe H, Ohuchi N, Miyata K, Kobori T, Odawara S, Kadowaki Y, Yokoyama S, Yamauchi T, Kadowaki T. : AdipoR agonist increases insulin sensitivity and exercise endurance in AdipoR-humanized mice. Commun.Biol.4(1):45, 2021
15. Iwabu M, Yamauchi T, Shimomura I, Eguchi K, Ogawa Y: Perceptions, attitudes and barriers to obesity management: Japanese data from the ACTION-IO study. J. Diabetes Investig. 12:845-858, 2021
16. Kato A, Fujimaki Y, Fujimori S, Isogawa A, Onishi Y, Suzuki R, Ueki K, Yamauchi T, Kadowaki T, Hashimoto Associations between diabetes duration and self-stigma development in Japanese people with type 2 diabetes: a secondary analysis of cross-sectional data. BMJ Open. 11: e055013, 2021
17. Kawai Y, Sankoda A, Waki K, Miyake K, Hayashi A, Mieno M, Wakui H, Tsurutani Y,

Saito J, Hirawa N, Yamakawa T, Komiya S, Isogawa A, Satoh S, Minami T, Osada U, Iwamoto T, Takano T, Terauchi Y, Tamura K, Yamauchi T, Kadowaki T, Nangaku M, Kashihara N, Ohe K. Efficacy of the Self-management Support System DialBetesPlus for Diabetic Kidney Disease: Protocol for a Randomized Controlled Trial. MIR Res Protoc. 10: e31061, 2021

18. Koseki M, Yamashita S, Ogura M, Ishigaki Y, Ono K, Tsukamoto K, Hori M, Matsuki K, Yokoyama S, Harada-Shiba M; Committee on Primary Dyslipidemia under the Research Program on Rare and Intractable Disease of the Ministry of Health, Labour and Welfare of Japan. Current Diagnosis and Management of Tangier Disease. *J Atheroscler Thromb.* 2021 May 14. doi: 10.5551/jat.RV17053
19. Koyama S, Sekijima Y, Ogura M, Hori M, Matsuki K, Miida T, Harada-Shiba M; Committee on Primary Dyslipidemia under the Research Program on Rare and Intractable Disease of the Ministry of Health, Labour and Welfare of Japan. Cerebrotendinous Xanthomatosis: Molecular Pathogenesis, Clinical Spectrum, Diagnosis, and Disease-Modifying Treatments. *J Atheroscler Thromb.* 2021 May 8. doi: 10.5551/jat.RV17055
20. Kubota N, Kubota T, Kadowaki T. Midlobular zone 2 hepatocytes: A gatekeeper of liver homeostasis. *Cell Metabolism* 33:855-856, 2021.
21. Kurakawa KI, Okada A, Manaka K, Konishi T, Jo T, Ono S, Uda K, Michihata N, Matsui H, Fushimi K, Yamaguchi S, Yamauchi T, Nangaku M, Yasunaga H, Kadowaki T. Clinical Characteristics and Incidences of Benign and Malignant Insulinoma Using a National Inpatient Database in Japan. J Clin Endocrinol Metab. 106: 3477-3486, 2021
22. Kuroda M, Bujo H, Yokote K, Murano T, Yamaguchi T, Ogura M, Ikewaki K, Koseki M, Takeuchi Y, Nakatsuka A, Hori M, Matsuki K, Miida T, Yokoyama S, Wada J, Harada-Shiba M; Committee on Primary Dyslipidemia under the Research Program on Rare and Intractable Disease of the Ministry of Health, Labour and Welfare of Japan. Current Status of Familial LCAT Deficiency in Japan. *J Atheroscler Thromb.* 2021 Apr 18. doi: 10.5551/jat.RV17051
23. Local Burden of Disease Vaccine Coverage Collaborators (incl Yamda T). Mapping routine measles vaccination in low- and middle-income countries. Nature. 2021 Jan;589(7842):415-419.
24. Momose A, Yamaguchi S, Okada A, Ikeda-Kurakawa K, Namiki D, Nannya Y, Kato H, Yamauchi T, Nangaku M, Kadowaki T. Factors associated with long-term care certification in older adults: a cross-sectional study based on a nationally representative survey in Japan. BMC Geriatr. 21:374, 2021
25. Nohara A, Tada H, Ogura M, Okazaki S, Ono K, Shimano H, Daida H, Dobashi K, Hayashi T, Hori M, Matsuki K, Minamino T, Yokoyama S, Harada-Shiba M; Committee on Primary Dyslipidemia under the Research Program on Rare and Intractable Disease of the Ministry of Health, Labour and Welfare of Japan. Homozygous Familial Hypercholesterolemia. *J Atheroscler Thromb.* 2021 Apr 18. doi: 10.5551/jat.RV17050
26. Ochiai T, Sano T, Nagayama T, Kubota N, Kadowaki T, Wakabayashi T, Iwatsubo T. Differential involvement of insulin receptor substrate (IRS)-1 and IRS-2 in brain insulin signaling is associated with the effects on amyloid pathology in a mouse model of Alzheimer's disease. *Neurobiol. Dis.*, in press, 2021.
27. Ogura M, Harada-Shiba M, Masuda D, Arai H, Bujo H, Ishibashi S, Daida H, Koga N, Oikawa S, Yamashita S; FAME Study Group. Factors Associated with Carotid Atherosclerosis and Achilles Tendon Thickness in Japanese Patients with Familial Hypercholesterolemia: A Subanalysis of the Familial Hypercholesterolemia Expert Forum (FAME) Study. *J Atheroscler Thromb.* 2021 Jun 10. doi: 10.5551/jat.62925
28. Ohn J, Been KW, Kim JY, Kim EJ, Park T, Yoon HJ, Ji JS, Okada-Iwabu M, Iwabu M, Yamauchi T, Kim YK, Seok C, Kwon O, Kim KH, Lee HH, Chung JH: Discovery of a transdermally deliverable pentapeptide for activating AdipoR1 to promote hair growth. EMBO Mol. Med. e13790, 2021

29. Okada A, Ono S, Yamaguchi S, Yamana H, Ikeda Kurakawa K, Michihata N, Matsui H, Nangaku M, Yamauchi T, Yasunaga H, Kadowaki T. Association between nutritional guidance or ophthalmological examination and discontinuation of physician visits in patients with newly diagnosed diabetes: a retrospective cohort study using a nationwide database. J Diabetes Investig.12:1619-1631, 2021
30. Okada A, Yamana H, Morita K, Sato Y, Yamaguchi S, Kurakawa KI, Michihata N, Matsui H, Fushimi K, Nangaku M, Yamauchi T, Yasunaga H, Kadowaki T. Potassium Concentration in Initial Fluid Therapy and In-Hospital Mortality of Patients with Diabetic Ketoacidosis. J Clin Endocrinol Metab. 106: e2162-e2175, 2021
31. 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. S1051-2276. 00160-6, 2021
32. Okazaki H, Gotoda T, Ogura M, Ishibashi S, Inagaki K, Daida H, Hayashi T, Hori M, Masuda D, Matsuki K, Yokoyama S and Harada-Shiba M on behalf of the Committee on Primary Dyslipidemia under the Research Program on Rare and Intractable Disease of the Ministry of Health, Labour and Welfare of Japan : Current Diagnosis and Management of Primary Chylomicronemia. *J Atheroscler Thromb*, accepted for publication on March 20, 2021.
33. Okazaki H, Gotoda T, Ogura M, Ishibashi S, Inagaki K, Daida H, Hayashi T, Hori M, Masuda D, Matsuki K, Yokoyama S, Harada-Shiba M; Committee on Primary Dyslipidemia under the Research Program on Rare and Intractable Disease of the Ministry of Health, Labour and Welfare of Japan. Current Diagnosis and Management of Primary Chylomicronemia. *J Atheroscler Thromb.* 2021 May 13. doi: 10.5551/jat.RV17054
34. Sakaue S, Kanai M, Tanigawa Y, Karjalainen J, Kurki M, Koshiba S, Narita A, Konuma T, Yamamoto K, Akiyama M, Ishigaki K, Suzuki A, Suzuki K, Obara W, Yamaji K, Takahashi K, Asai S, Takahashi Y, Suzuki T, Shinozaki N, Yamaguchi H, Minami S, Murayama S, Yoshimori K, Nagayama S, Obata D, Higashiyama M, Masumoto A, Koretsune Y; FinnGen, Ito K, Terao C, Yamauchi T, Komuro I, Kadowaki T, Tamiya G, Yamamoto M, Nakamura Y, Kubo M, Murakami Y, Yamamoto K, Kamatani Y, Palotie A, Rivas MA, Daly MJ, Matsuda K, Okada Y. A cross-population atlas of genetic associations for 220 human phenotypes. Nat Genet. 53:1415-1424, 2021
35. Sakurai Y, Kubota N, Yamauchi T, Kadowaki T. Role of Insulin Resistance in MAFLD. Int J Mol Sci. 2021 Apr 16;22(8):4156.
36. Sasako T, Tanaka T, Yamauchi T. Adaptive Response as a Potential Key Link Between SGLT2 Inhibition and Renoprotection. Kidney Int Rep 6(8): 2022-2024, 2021.
37. Sasako T, Ueki K. ER Stress Response Failure and Steatohepatitis Comorbid with Diabetes. Psychology and Patho-physiological Outcomes of Eating, IntechOpen Ltd., UK, 2021. doi: 10.5772/intechopen.100054.
38. Sasako T, Ueki K, Miyake K, Okazaki Y, Takeuchi Y, Ohashi Y, Noda M, Kadowaki T.: Effect of a Multifactorial Intervention on Fracture in Patients With Type 2 Diabetes: Subanalysis of the J-DOIT3 Study. J Clin Endocrinol Metab 106(5): e2116-e2128, 2021.
39. Sawada M*, Kubota N*, Sekine R, Yakabe M, Kojima T, Umeda-Kameyama Y, Usami S, Akishita M, Ogawa S. Sex-related differences in the effects of nutritional status and body composition on functional disability in the elderly. *PLoS One* 16:e0246276, 2021 (*co-first authors).
40. Tada H, Nomura A, Ogura M, Ikewaki K, Ishigaki Y, Inagaki K, Tsukamoto K, Dobashi K, Nakamura K, Hori M, Matsuki K, Yamashita S, Yokoyama S, Kawashiri MA, Harada-Shiba M; Committee on Primary Dyslipidemia under the Research Program on Rare and Intractable Desease of the Ministry of Health, Labour and

Welfare of Japan. Diagnosis and Management of Sitosterolemia 2021. *J Atheroscler Thromb.* 2021 Apr 28. doi: 10.5551/jat.RV17052

41. Takahashi M, Okazaki H, Ohashi K, Ogura M, Ishibashi S, Okazaki S, Hirayama S, Hori M, Matsuki K, Yokoyama S, Harada-Shiba M; Committee on Primary Dyslipidemia under the Research Program on Rare and Intractable Disease of the Ministry of Health, Labour and Welfare of Japan. Current Diagnosis and Management of Abetalipoproteinemia. *J Atheroscler Thromb.* 2021 May 16. doi: 10.5551/jat.RV17056
42. Takeuchi F, Liang YQ, Isono M, Tajima M, Cui ZH, Iizuka Y, Gotoda T, Nabika T, Kato N: Integrative genomic analysis of blood pressure and related phenotypes in rats. Dis Model Mech. 2021 May 1;14(5)
43. Tanaka Y, Shimanaka Y, Caddeo A, Kubo T, Mao Y, Kubota T, Kubota N, Yamauchi T, Mancina RM, Baselli G, Luukkonen P, Pihlajamäki J, Yki-Järvinen H, Valenti L, Arai H, Romeo S, Kono N. LPIAT1/MBOAT7 depletion increases triglyceride synthesis fueled by high phosphatidylinositol turnover. *Gut* 70:180-193, 2021.
44. Tateishi R, Matsumura T, Okanoue T, Shima T, Uchino K, Fujiwara N, Senokuchi T, Kon K, Sasako T, Taniai M, Kawaguchi T, Inoue H, Watada H, Kubota N, Shimano H, Kaneko S, Hashimoto E, Watanabe S, Shiota G, Ueki K, Kashiwabara K, Matsuyama Y, Tanaka H, Kasuga M, Araki E, Koike K.: LUCID study investigators: Hepatocellular carcinoma development in diabetic patients: a nationwide survey in Japan. J Gastroenterol 56(3): 261-273, 2021.
45. Tian J, Chung HK, Moon JS, Nga HT, Lee HY, Kim JT, Chang JY, Kang SG, Ryu D, Che X, Choi JY, Tsukasaki M, Sasako T, Lee SH, Shong M, Yi HS. Skeletal muscle mitoribosomal defects are linked to low bone mass caused by bone marrow inflammation in male mice. J Cachexia Sarcopenia Muscle, Online ahead of print.
46. Ueki K, Sasako T, Okazaki Y, Miyake K, Nangaku M, Ohashi Y, Noda M, Kadowaki T.: the J-DOIT3 Study Group: Multifactorial intervention has a significant effect on diabetic kidney disease in patients with type 2 diabetes. Kidney Int 99(1): 256-266, 2021.
47. Waki H, Yamauchi T.: Body-weight-independent glucose-lowering effect of the β3-adrenergic receptor agonist mirabegron in humans. J Diabetes Investig. 2021 May;12(5):689-690. doi: 10.1111/jdi.13509. Epub 2021 Feb 24.
48. Watanabe D, Murakami H, Ohno H, Tanisawa K, Konishi K, Todoroki-Mori K, Tsunematsu Y, Sato M, Ogata Y, Miyoshi N, Kubota N, Kunisawa J, Wakabayashi K, Kubota T, Watanabe K, Miyachi M. Stool pattern is associated with not only the prevalence of tumorigenic bacteria isolated from fecal matter but also plasma and fecal fatty acids in healthy Japanese adults. *BMC Microbiol.* 21: 196, 2021.
49. Yamashita S, Masuda D, Harada-Shiba M, Arai H, Bujo H, Ishibashi S, Daida H, Koga N, Oikawa S; FAME Study Group. Effectiveness and Safety of Lipid-Lowering Drug Treatments in Japanese Patients with Familial Hypercholesterolemia: Familial Hypercholesterolemia Expert Forum (FAME) Study. *J Atheroscler Thromb.* 2021 May 13. doi: 10.5551/jat.62764
50. Yamazaki T, Inada S, Sawada M, Sekine R, Kubota N, Fukatsu K, Yoshiuchi K. Diets with high carbohydrate contents were associated with refeeding hypophosphatemia: A retrospective study in Japanese inpatients with anorexia nervosa. *Int. J. Eat. Disord.* 54:88-94, 2021.

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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 9 assistant professors.

Clinical activities

On the average, 60-70 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 60-65 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 are performed under the admission of Patient Relations and Clinical Ethics Center. Cord blood cells are also used as a source of hematopoietic stem cells.

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. Ebisawa K, Shimura A, Honda A, Masamoto Y, Nakahara F, and Kurokawa M. Hemoglobin and C-reactive protein levels as predictive factors for long-term successful glucocorticoid treatment for multicentric Castleman's disease. Leukemia and Lymphoma 62(3): 614-619, 2021.
2. Kurihara Y, Taoka K, Takagi E, Toyama K, Nakazaki K, and Kurokawa M. Treatment of secondary immune thrombocytopenia with non-Hodgkin lymphoma: A case report and literature review. Internal Medicine 60(10): 1583-1588, 2021.
3. Kato H, Koga M, Kobayashi H, Maki H, Ikemura M, Kurokawa M, Nangaku M, Makita N, and Ito N. Primary bone adult T-cell lymphoma with multiple skeletal lesions and debilitating painful osteolysis: A case report. Osteoporosis International 32(5): 1013-1017, 2021.
4. Kawai M, Mano Tatsuo, Naito T, Honda A, Nakai Y, Toyama K, Fujioka Y, Makise N, Hasegawa H, Sakuishi K, Kurokawa M, and Toda T. Disseminated necrotizing leuko-encephalopathy after allogeneic peripheral blood stem cell transplantation and methotrexate administration. Neurology and Clinical Neuro-science 9:155–156, 2021.
5. Maki H, Yoshimi A, Shimada T, Arai S, Nakahara F, Morita K, Kamikubo Y, Ikegawa M, and Kurokawa M. Physical interaction between BAALC and DBN1 induces chemoresistance in leukemia. Experimental Hematology 94:31-36, 2021.
6. Sasaki K, Matsuda K, Miyauchi M, Honda A, Shimura A, Masamoto Y, and Kurokawa M. A retrospective analysis on arteritis after administration of granulocyte colony-stimulating factor. Annals of Hematology 100(5): 1341-1343, 2021.
7. Matsuda K, Jo T, Miyauchi M, Toyama K, Nakazaki K, Matsui H, Fushimi K, Yasunaga H, and Kurokawa M. Difference of preventing effects of G-CSF according to age in patients with malignant lymphoma: a nation-wide analysis in Japan. Journal of Infection and Chemotherapy, S1341-321X(21): 00078-7, 2021.
8. Takezaki T, Nakazaki K, Toyama K, Matsuda K, Honda A, and Kurokawa M. Reduction of cycles of bendamustine plus rituximab therapy in the cases with good response for indolent B-cell lymphomas. Hematological Oncology, 2021 May 2. doi: 10.1002/hon.2871.
9. Ito K, Ito J, Yamamoto Y, Nakajima R, Fujii M, Katakura Y, Muramatsu A, Takayashiki N, Toyama K, Kurokawa M, and Hiroaki Yagyu. Serial assessments of anterior pituitary hormones in a case of mixed histiocytosis representing Langerhans cell histiocytosis overlapping with Erdheim–Chester disease. Endocrinol Diabetes Metab Case Rep. 2021 May 1;2021:EDM210030. doi: 10.1530/EDM-21-0030.
10. Masamoto Y, Shimura A, and Kurokawa M. Reduced bendamustine for elderly patients with follicular lymphoma. Annals of Haematology, 101(3): 713–715, 2022.
11. Ito Y, Honda A, and Kurokawa M. Impact of vitamin D level at diagnosis and transplantation on the prognosis of hematological malignancy: a systematic review and meta-analysis. Blood Advances, 6(5):1499-1511, 2022.
12. Homan CC, King-Smith SL, Lawrence DM, Arts P, Feng J, Andrews J, Armstrong M, Ha T, Dobbins J, Drazer MW, Yu K, Bödör C, Cantor A, Cazzola M, Degelman E, DiNardo CD, Duployez N, Favier R, Fröhling S, Fitzgibbon J, 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, Liu P, Godley LA, Schreiber AW, Hahn CN, Scott HS, and Brown AL. On behalf of the RUNX1 international data-sharing consortium. The RUNX1 database (RUNX1db): establish-ment of an expert curated RUNX1 registry and genomics database as a publicc resource for familial platelet disorder with myeloid malignan-cy. Haematologica, 106(11):3004-3007, 2021.
13. Miyauchi M, Sasaki K, Kagoya Y, Taoka K, Masamoto Y, Yamazaki S, Arai S, Mizuno H, and Kurokawa M. CAMK2G is identified as a novel therapeutic target for myelofibrosis. Blood Advances, 6(5):1585-1597, 2022.
14. Hanata N, Shoda H, Kono M, Komai T,

Natsumoto B, Tsuchida Y, Tsuchiya H, Nagafuchi Y, Taoka K, Kurokawa M, and Fujio K. Immature platelet levels correlate with disease activity and predict treatment response of thrombocytopenia in lupus patients. Lupus, 30(11):1764-1772, 2021.

15. Yoshioka K, Kurokawa R, Amemiya S, Matsuda K, Honda A, Kurokawa M, Shinozaki-Ushiku A, and Abe O. Rapidly progressed blastic plasmacytoid dendritic cell neoplasm causing diffuse skin thickening: a case report with sequential CT examinations. Radiology Case Reports, 16(10):2929-2933, 2021.
16. Matsuda K, Ise M, Shimura A, Honda A, Masamoto Y, Jo T, Yasunaga H, and Kurokawa M. Use of wide-spectrum antimicrobials with blood culture tests during chemotherapy as an accurate marker of febrile neutropenia in the DPC database: A validation study. Journal of Infection and Chemotherapy, (10):1541-1542, 2021.
17. Matsuda K, Jo T, Toyama K, Nakazaki K, Matsui H, Fushimi K, Yasunaga H, and Kurokawa M. Risk factors for early in-hospital death in patients who developed coagulopathy during induction therapy for acute promyelocytic leukemia: a nation-wide analysis in Japan. Annals of Hematology, 100(10):2613-2619, 2021.
18. Honda A, Koya J, Yoshimi A, Miyauchi M, Taoka K, Kataoka K, Arai S, and Kurokawa M. Loss-of-function mutations in BCOR contribute to chemotherapy resistance in acute myeloid leukemia. Experimental Hematology, 101-102: 42-48.e11, 2021.
19. Mizuno H, Koya J, Masamoto Y, Kagoya Yuki, and Kurokawa M. Evi1 upregulates Fbp1 and supports progression of acute myeloid leukemia through pentose phosphate pathway activation. Cancer Science, 112(10):4112-4126, 2021.
20. Kato K, Yabe H, Shimozawa N, Adachi S, Kurokawa M, Hashii Y, Sato A, Yoshida N, Kaga M, Onodera O, Kato S, Atsuta Y, and Morio T. Stem cell transplantation for pediatric patients with adrenoleukodystrophy: a nation-wide retrospective analysis in Japan. Pediatric Transplantation, 26(1):e14125, 2022.
21. Hirano Y, Miyawaki S, Tanaka S, Taoka K, Hongo H, Teranishi Y, Takami H, Takayanagi S, Kurokawa M, and Saito N. Clinical features and prognostic factors for primary anaplastic large cell lymphoma of the central nervous system: a systematic review. Cancers, 13(17): 4358, 2021.
22. Murakami D, Maki H, Matsuda K, Masamoto Y, Suzuki F, Amemiya S, Osawa K, Hinata M, Ikemura M, Ushiku T, and Kurokawa M. Cerebral Toxoplasmosis complicating lympho-plasmacytic lymphoma in partial remission. Journal of Infection and Chemotherapy, 28(2): 279-282, 2022.
23. Miyauchi M, Ito Y, Nakahara F, Hino T, Nakamura F, Iwasaki Y, Kawagoshi T, Koya J, Yoshimi A, Arai S, Kagoya Y, and Kurokawa M. Efficient production of human neutrophils from iPSCs that prevent murine lethal infection with immune cell recruitment. Blood, 138(24):2555-2569, 2021.
24. Takano H, Yasunaga M, Yamazaki I, Nishikawa M, Masamoto Y, Kawakami M, Yatomi Y, and Kurokawa M. Degenerated mitochondria in leukemic blast appeared as granules on May-Grunwald-Giemsa staining. Annals of Hematology, 101(5):1135-1136, 2022.
25. Ito Y, Nakahara F, Kagoya Y, and Kurokawa M. CD62L expression level determines the cell fate of myeloid progenitors. Stem Cell Reports, 16(12):2871-2886, 2021.

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Introduction and Organization

The Department of Allergy and Rheumatology presently consists of 13 staffs mentioned above, who preside over 3 medical staff, 14 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 East Hospital Ward and the research rooms are located in the East Hospital Ward, the Central 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
2. Analysis of newly-identified regulatory T cell subset and inhibitory cytokines, and its roles in autoimmune diseases.
3. Analysis of T cell and B cell repertoires in autoimmune diseases.
4. Analysis of autoimmune associated gene functions in mice and human models.
5. Analysis of signal transduction mechanisms in autoimmune diseases.
6. Analysis of autoimmune disease-specific iPS cells
7. Exploration of the roles of protein prenylation in the animal models of lung disease.
8. Analysis of bone strength in glucocorticoid-induced osteoporosis.
9. Investigation of biomarkers in autoimmune disease.

Publications

1. Clinical remission of rheumatoid arthritis in a multicenter real-world study in Asia-Pacific region. Sun X, Li R, Cai Y, Al-Herz A, Lahiri M, Choudhury MR, Hidayat R, Suryana BPP, Kaneko Y, Fujio K, Van Hung N, Pandya S, Pang LK, Katchamart W, Sigdel KR, Paudyal B, Narongroeknawin P, Chevaisrakul P, Sun F, Lu Y, Ho C, Yeap SS, Li Z; APLAR RA SIG group. **Lancet Reg Health West Pac.** 2021;15:100240.
2. Serum Amphiregulin and Heparin-Binding Epidermal Growth Factor as Biomarkers in Patients with Idiopathic Inflammatory Myopathy. Hanata N, Nagafuchi Y, Sugimori Y, Kobayashi S, Tsuchida Y, Iwasaki Y, Shoda H, Fujio K. **J Clin Med.** 2021;10(16):3730.
3. Immature platelet levels correlate with disease activity and predict treatment response of thrombocytopenia in lupus patients. Hanata N, Shoda H, Kono M, Komai T, Natsumoto B, Tsuchida Y, Tsuchiya H, Nagafuchi Y, Taoka K, Kurokawa M, Fujio K. **Lupus.** 2021;30(11): 1764-1772.
4. ANCA-associated vasculitis with protein-losing enteropathy is characterized by hypocomplementemia. Goto M, Tsuchida Y, Terada K, Takahashi H, Sugimori Y, Komai T, Iwasaki Y, Shoda H, Fujio K. **Rheumatol Int.** 2021 Jun 22. doi: 10.1007/s00296-021-04923-2
5. Nailfold capillaroscopic abnormalities in angioedema with eosinophilia. Tsuzuki S, Komai T, Terada K, Tsuchida Y, Tanaka M, Tateishi Y, Shinozaki-Ushiku A, Shoda H, Fujio K. **Allergol Int.** 2021;70(4):501-503.
6. Dynamic landscape of immune cell-specific gene regulation in immune-mediated diseases. Ota M, Nagafuchi Y, Hatano H, Ishigaki K, Terao C, Takeshima Y, Yanaoka H, Kobayashi S, Okubo M, Shirai H, Sugimori Y, Maeda J, Nakano M,

Yamada S, Yoshida R, Tsuchiya H, Tsuchida Y, Akizuki S, Yoshifuji H, Ohmura K, Mimori T, Yoshida K, Kurosaka D, Okada M, Setoguchi K, Kaneko H, Ban N, Yabuki N, Matsuki K, Mutoh H, Oyama S, Okazaki M, Tsunoda H, Iwasaki Y, Sumitomo S, Shoda H, Kochi Y, Okada Y, Yamamoto K, Okamura T, Fujio K. **Cell.** 2021; 184(11):3006-3021.e17

7. Multiomics landscape of synovial fibroblasts in rheumatoid arthritis. Tsuchiya H, Ota M, Fujio K. **Inflamm Regen.** 2021;41(1):7.
8. Identifying the most influential gene expression profile in distinguishing ANCA-associated vasculitis from healthy controls. Yanaoka H, Nagafuchi Y, Hanata N, Takeshima Y, Ota M, Suwa Y, Shirai H, Sugimori Y, Okubo M, Kobayashi S, Hatano H, Yamada S, Tsuchida Y, Iwasaki Y, Sumitomo S, Shoda H, Okada M, Okamura T, Yamamoto K, Fujio K. **J Autoimmun.** 2021 May;119:102617.
9. Parsing multiomics landscape of activated synovial fibroblasts highlights drug targets linked to genetic risk of rheumatoid arthritis. Tsuchiya H, Ota M, Sumitomo S, Ishigaki K, Suzuki A, Sakata T, Tsuchida Y, Inui H, Hirose J, Kochi Y, Kadono Y, Shirahige K, Tanaka S, Yamamoto K, Fujio K. **Ann Rheum Dis.** 2021; 80(4):440-450.
10. Contribution of a European-Prevalent Variant near CD83 and an East Asian-Prevalent Variant near IL17RB to Herpes Zoster Risk in Tofacitinib Treatment: Results of Genome-Wide Association Study Meta-Analyses. Bing N, Zhou H, Chen X, Hirose T, Kochi Y, Tsuchida Y, Ishigaki K, Sumitomo S, Fujio K, Zhang B, Valdez H, Vincent MS, Martin D, Clark JD. **Arthritis Rheumatol.** 2021 Jul;73(7):1155-1166.

Department of Infectious Diseases (Internal Medicine)

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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 of the internal medicine for under-graduate medical students according to the education-al 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 bed-side teaching 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 HIV infection: we have made a great contribution in the establishment of the guideline for treatment of HIV infection in Japan.
(2) 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.
(3) 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.
(4) 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.
(5) Innovation of new methods to control viral hepatitis or prevent the development of hepatocellular carcinoma in chronic viral hepatitis.
(6) Establishment of the effective infection control method and therapy of MRSA and other MDRO infection.
(7) Elucidating the mechanism and signal transduction of bacterial infection through toll-like receptors.
(8) Establishment of effective diagnosis methods and therapy for *C. difficile* infection
(9) Clinical research on COVID-19.

References

1. Hangai S, Kawamura T, Kimura Y, Chang CY, Hibino S, Yamamoto D, et al. Orchestration of myeloid-derived suppressor cells in the tumor microenvironment by ubiquitous cellular protein TCTP released by tumor cells. Nat Immunol. 2021;22(8):947-57.
2. Harada S, Aoki K, Ohkushi D, Okamoto K, Takehana K, Akatsuchi T, et al. Institutional outbreak involving multiple clades of IMP-producing Enterobacter cloacae complex sequence type 78 at a cancer center in Tokyo, Japan. BMC Infect Dis. 2021;21(1):289.
3. Hirano J, Yoshio S, Sakai Y, Songling L, Suzuki T, Itoh Y, et al. Hepatitis C virus modulates signal peptide peptidase to alter host protein processing. Proc Natl Acad Sci U S A. 2021;118(22).
4. Ikeda M, Kobayashi T, Fujimoto F, Okada Y, Higurashi Y, Tatsuno K, et al. The prevalence of the iutA and ibeA genes in Escherichia coli isolates from severe and non-severe patients with bacteremic acute biliary tract infection is significantly different. Gut Pathog. 2021;13(1):32.
5. Ikeda M, Wakabayashi Y, Okamoto K, Yanagimoto S, Okugawa S, Moriya K. Changing trends in lipid profile and biomarkers of renal function and bone metabolism before and after switching from tenofovir disoproxil fumarate to tenofovir alafenamide: a prospective observational study. AIDS Res Ther. 2021;18(1):30.
6. Ikeuchi K, Okamoto K, Inoue N, Okugawa S, Moriya K. Chronic Disseminated Gonococcal Infection in a Japanese Man with Novel C5 Gene Mutation. J Clin Immunol. 2021;41(3):691-3.
7. Ishihara Y, Okamoto K, Shimosaka H, Ono Y,

Kanno Y, Ikeda M, et al. Prevalence and clinical characteristics of patients with biologically false-positive reactions with serological syphilis testing in contemporary practice: 10-year experience at a tertiary academic hospital. Sex Transm Infect. 2021;97(6):397-401.

8. Ito H, Okamoto K, Yamamoto S, Yamashita M, Kanno Y, Jubishi D, et al. Incidence and Risk Factors for Inappropriate Use of Non-Culture-Based Fungal Assays: Implication for Diagnostic Stewardship. Open Forum Infect Dis. 2022;9(1): ofab601.
9. Jubishi D, Okamoto K, Hamada K, Ishii T, Hashimoto H, Shinohara T, et al. The association between adverse reactions and immune response against SARS-CoV-2 spike protein after vaccination with BNT162b2 among healthcare workers in a single healthcare system: a prospective observational cohort study. Hum Vaccin Immunother. 2022;18(5):2048559.
10. Kitaura S, Okamoto K, Wakabayashi Y, Okada Y, Okazaki A, Ikeda M, et al. A Cold-Blooded Tiptoer: Nonresolving Cellulitis in an Immuno-compromised Patient. Open Forum Infect Dis. 2022;9(4):ofac074.
11. Kobayashi T, Ikeda M, Okada Y, Higurashi Y, Okugawa S, Moriya K. Clinical and Microbiological Characteristics of Recurrent Escherichia coli Bacteremia. Microbiol Spectr. 2021;9(3):e0139921.
12. Kurano M, Ohmiya H, Kishi Y, Okada J, Nakano Y, Yokoyama R, et al. Measurement of SARS-CoV-2 Antibody Titers Improves the Prediction Accuracy of COVID-19 Maximum Severity by Machine Learning in Non-Vaccinated Patients. Front Immunol. 2022;13:811952.
13. Minami T, Tateishi R, Fujiwara N, Nakagomi R, Nakatsuka T, Sato M, et al. Impact of Obesity and Heavy Alcohol Consumption on Hepato-cellular Carcinoma Development after HCV Eradication with Antivirals. Liver Cancer. 2021; 10(4):309-19.
14. Mizoguchi M, Harada S, Okamoto K, Higurashi Y, Ikeda M, Moriya K. Comparative performance and cycle threshold values of 10 nucleic acid amplification tests for SARS-CoV-2 on clinical samples. PLoS One. 2021;16(6):e0252757.
15. Nakano Y, Kurano M, Morita Y, Shimura T, Yokoyama R, Qian C, et al. Time course of the sensitivity and specificity of anti-SARS-CoV-2 IgM and IgG antibodies for symptomatic COVID-19 in Japan. Sci Rep. 2021;11(1):2776.
16. Nishikawa H, Shiraki M, Hiramatsu A, Hara N, Moriya K, Hino K, et al. Reduced handgrip strength predicts poorer survival in chronic liver diseases: A large multicenter study in Japan. Hepatol Res. 2021;51(9):957-67.
17. Nomura Y, Okamoto K, Ohama Y, Higurashi Y, Harada S, Moriya K. Tenosynovitis caused by Mycobacterium marseillense, initially identified as Mycobacterium avium complex using AccuProbe and COBAS TaqMan. BMC Infect Dis. 2021;21(1):1092.
18. Ohama Y, Aoki K, Harada S, Nagasawa T, Sawabe T, Nonaka L, et al. Genetic Environment Surrounding blaOXA-55-like in Clinical Isolates of Shewanella algae Clade and Enhanced Expression of blaOXA-55-like in a Carbapenem-Resistant Isolate. mSphere. 2021;6(5):e0059321.
19. Okushin K, Suzuki R, Tsutsumi T, Okamoto K, Ikeuchi K, Kado A, et al. Change in hepatitis C virus positivity among needle-stick injury source patients: a 10-year experience in a Japanese tertiary hospital. BMC Infect Dis. 2021;21(1): 399.
20. Osawa I, Okamoto K, Ikeda M, Otani A, Wakimoto Y, Yamashita M, et al. Dynamic changes in fibrinogen and D-dimer levels in COVID-19 patients on nafamostat mesylate. J Thromb Thrombolysis. 2021;51(3):649-56.
21. Oyama Y, Yasunaga M, Honda A, Maki H, Masamoto Y, Kobayashi T, et al. Severe cellulitis caused by Achromobacter xylosoxidans after allogeneic hematopoietic stem cell transplanta-tion. J Infect Chemother. 2021;27(5):770-2.
22. Sato Y, Atarashi K, Plichta DR, Arai Y, Sasajima S, Kearney SM, et al. Novel bile acid biosynthetic pathways are enriched in the microbiome of centenarians. Nature. 2021; 599(7885):458-64.
23. Shimura T, Kurano M, Kanno Y, Ikeda M, Okamoto K, Jubishi D, et al. Clot waveform of APTT has abnormal patterns in subjects with COVID-19. Sci Rep. 2021;11(1):5190.

24. Shimura T, Kurano M, Okamoto K, Jubishi D, Kano K, Igarashi K, et al. Increase in serum levels of phosphatidylserine-specific phospholipase A1 in COVID-19 patients. Cell Mol Immunol. 2021;18(9):2275-7.
25. Yamashita M, Ikeda M, Kato I, Ohama Y, Ando M, Ikemura M, et al. Protothecosis in the mucosa of the pharynx mimicking pharyngeal cancer in an immunocompetent individual: a case report. Ann Clin Microbiol Antimicrob. 2022;21(1):5.
26. Yokoyama R, Kurano M, Morita Y, Shimura T, Nakano Y, Qian C, et al. Validation of a new automated chemiluminescent anti-SARS-CoV-2 IgM and IgG antibody assay system detecting both N and S proteins in Japan. PLoS One. 2021; 16(3):e0247711.

Department of Stress Science and Psychosomatic Medicine

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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 covers eating disorder, panic disorder, and various psychosomatic diseases such as chronic headache, irritable bowel syndrome, functional dyspepsia, hypertension, diabetes mellitus, and hyperthyroidism. Our teaching staff consists of one associate professor, one associate, one research associate, and 5 adjunct professors, and other members are 4 senior residents, 15 graduate students, and 4 researchers.

Clinical activities

Our department is responsible for both outpatient clinic and inpatient ward. The ward is managed as a part of the Division of General Internal Medicine, and senior residents, an associate, and the associate professor attend it every day and provide close side-by-side instruction to junior residents. The weekly professor's round is scheduled on Thursday morning. During 2021 April to 2022 March, overall 2,453 patients (99 individuals) were admitted to the ward, most of whom were eating disorder patients. Outpatient clinic is attended on every morning and afternoon in three consultation rooms by approximately fifteen physicians. During 2021 April to 2022 March, the numbers of the new outpatients and of the overall outpatients in our department were 172 and 4,847, respectively.

Teaching activities

We are giving 6 methodical lectures on psychosomatic medicine for fourth grade medical students, 'clinical clerkship' for fifth grade students lasting two weeks, 'advanced clinical clerkship' for 3 to 4 fifth grade students lasting 4 weeks each, and clinical lectures on psychosomatic diseases in cardiology for fifth grade students and on eating disorders for sixth grade students. We are trying to teach them not only basic knowledge of specific diseases, ways of physical examination, or interpretation of laboratory data, but also relevant ways of clinical interview, doctor-patient relationship building, and behavior modification.

As for education for junior residents, our senior residents and an associate provide man-to-man instruction. In addition, they can learn how to present the history of newly-admitted patients at the weekly professor's round from our teaching staff.

Research activities

Targeting stress-related diseases such as not only

those covered by our department but also other lifestyle-related disease, and cancers, we are investigating their pathophysiology and psycho-pathology through assessing bio-psycho-behavioral time-series data, various questionnaire data, and autonomic nervous function. We are also actively conducting basic as well as clinical research on eating-related substances.

Some representative research methods are as follows:

1) Ecological momentary assessment (EMA): Investigation on neurobehavioral basis of stress-related diseases such as tension-type headache, eating disorders, insomnia, and panic disorder using portable computers for real-time assessment of subjective symptoms in combination with ambulatory monitors such as electrocardiogram and actigraphy.
2) Neuroendocrinological and neuroimmunological studies in anorexia nervosa patients: multi-disciplinary investigation on energy metabolism during a 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 evaluating depressive mood in cancer patients.

Fifteen graduate students and 4 researchers actively conducted their researches along with our teaching staff. We have been also collaborating with many scientists belonging to other departments either in Japan or abroad. Research conferences are held once a month, where one of the graduate students presents his/her research for open discussion by all the members of our department.

References

1. Miyamoto S, Harashima S, Yoshiuchi K. Validating the family coping questionnaire for eating disorders for caregivers of Japanese patients with eating disorders: association between coping strategies and psychological characteristics. J Eat Disord. 2021 Dec 18;9(1): 163.
2. Shirane S, Michihata N, Yoshiuchi K, Ariyoshi K, Iwase S, Morita K, Matsui H, Fushimi K, Yasunaga H. Evaluation of quality indicators near death in older adult cancer decedents in Japan: A nationwide retrospective cohort study. Jpn J Clin Oncol. 2021 Nov 1;51(11):1643-1648.
3. Kurisu K, Yamanaka Y, Yamazaki T, Yoneda R, Otani M, Takimoto Y, Yoshiuchi K. A clinical course of a patient with anorexia nervosa receiving surgery for superior mesenteric artery syndrome. J Eat Disord. 2021 Jun 30;9(1):79.
4. Kurisu K, Yoshiuchi K. Comparison of Antipsychotics for the Treatment of Patients With Delirium and QTc Interval Prolongation: A Clinical Decision Analysis. Front Psychiatry. 2021 Jun 25;12:609678.
5. Inada S, Yoshiuchi K, Park S, Aoyagi Y. Trajectories of objectively measured physical activity and mood states in older Japanese adults: longitudinal data from the Nakanojo Study. Biopsychosoc Med. 2021 Feb 23;15(1):5.
6. Maeda I, Inoue S, Uemura K, Tanimukai H, Hatano Y, Yokomichi N, Amano K, Tagami K, Yoshiuchi K, Ogawa A, Iwase S; Phase-R Delirium Study Group. Low-Dose Trazodone for Delirium in Patients with Cancer Who Received Specialist Palliative Care: A Multicenter Prospective Study. J Palliat Med. 2021 Jun;24(6): 914-918.
7. Hamatani S, Hirano Y, Sugawara A, Isobe M, Kodama N, Yoshihara K, Moriguchi Y, Ando T, Endo Y, Takahashi J, Nohara N, Takamura T, Hori H, Noda T, Tose K, Watanabe K, Adachi H, Gondo M, Takakura S, Fukudo S, Shimizu E, Yoshiuchi K, Sato Y, Sekiguchi A. Eating Disorder Neuroimaging Initiative (EDNI): a multicentre prospective cohort study protocol for elucidating the neural effects of cognitive-behavioural therapy for eating disorders. BMJ Open. 2021 Jan 25;11(1):e042685.
8. Harashima S, Fujimori M, Akechi T, Matsuda T, Saika K, Hasegawa T, Inoue K, Yoshiuchi K, Miyashiro I, Uchitomi Y, J Matsuoka Y. Death by suicide, other externally caused injuries and cardiovascular diseases within 6 months of

cancer diagnosis (J-SUPPORT 1902). Jpn J Clin Oncol. 2021 Apr 30;51(5):744-752.
9. Yamazaki T, Inada S, Sawada M, Sekine R, Kubota N, Fukatsu K, Yoshiuchi K. Diets with high carbohydrate contents were associated with refeeding hypophosphatemia: A retrospective study in Japanese inpatients with anorexia nervosa. Int J Eat Disord. 2021 Jan;54(1):88-94.
10. Qian K, Koike T, Yoshiuchi K, Schuller BW, Yamamoto Y. Can Appliances Understand the Behavior of Elderly Via Machine Learning? A Feasibility Study. IEEE Internet of Things Journal. 2021;8(10):8343-55.
11. Otani M, Hiraide M, Horie T, Mitsui T, Yoshida T, Takamiya S, Sakuta R, Usami M, Komaki G, Yoshiuchi K. Psychometric properties of the Eating Disorder Examination-Questionnaire and psychopathology in Japanese patients with eating disorders. Int J Eat Disord. 2021 Feb;54(2):203-211.

Internal Medicine

3. Clinical Laboratory Medicine and Pathology

Department of Transfusion Medicine

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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 trans-plantation 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-tranfusional 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.

References

1. Yoshiko Tamai, Hitoshi Ohto, Hideto Takahashi, Junnichi Kitazawa[1)5)], for the Pediatric RBC Alloimmunization Consortium. Toshiyuki Ikeda, Yutaka Nagura, Hitoshi Okazaki, et al. Transfusion-related alloimmunization to red blood cell antigens in pediatric recipients **Transfusion Medicine Reviews** 2021 Jan;35(1):29-36.
2. Yuki Nakano, Makoto Kurano, Yoshifumi Morita, Takuya Shimura, Rin Yokoyama, Chungen Qian, Fuzhen Xia, Fan He, Yoshiro Kishi, Jun Okada, Naoyuki Yoshikawa, Yutaka Nagura, Hitoshi Okazaki, Kyoji Moriya, Yasuyuki Seto, Tatsuhiko Kodama, Yutaka Yatomi. Time course of the sensitivity and specificity of anti-SARS-CoV-2 IgM and IgG antibodies for symptomatic COVID-19 in Japan. **Scientific Reports** 2021 Feb 2;11(1):2776
3. Yokoyama R, Kurano M, Morita Y, Shimura T, Nakano Y, Qian C, Xia F, He F, Kishi Y, Okada J, Yoshikawa N, Nagura Y, Okazaki H, Moriya K, Seto Y, Kodama T, Yatomi Y. Validation of a new automated chemiluminescent anti-SARS-CoV-2 IgM and IgG antibody assay system detecting both N and S proteins in Japan. **PLOS ONE** 2021 Mar 4;16(3):e0247711

Reproductive, Developmental and Aging Sciences

1. Obstetrics and Gynecology

Department of Reproductive Endocrinology

Associate Professors

Takeshi Nagamatsu

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 2021

1. Katagiri Y, Jwa SC, Kuwahara A, Iwasa T, Ono M, Kato K, et al. Assisted reproductive technology in Japan: A summary report for 2019 by the Ethics Committee of the Japan Society of Obstetrics and Gynecology. Reprod Med Biol. 2021 Dec 14;21(1):e12434.
2. Kanda R, Miyagawa Y, Wada-Hiraike O, Hiraike H, Nagasaka K, Ryo E, et al. Ulipristal acetate simultaneously provokes antiproliferative and proinflammatory responses in endometrial cancer cells. Heliyon. 2021 Dec 29;8(1).
3. Kuji S, Harada M, Yoshioka N, Kajiyama H, Satoh T, Mikami M, et al. Survival and reproductive outcomes after fertility-sparing surgery performed for borderline epithelial ovarian tumor in Japanese adolescents and young adults: Results of a retrospective nationwide

study. J Obstet Gynaecol Res. 2022 Mar;48(3): 806-816.

4. Harada T, Osuga Y, Suzuki Y, Fujisawa M, Fukui M, Kitawaki J. Relugolix, an oral gonadotropin-releasing hormone receptor antagonist, reduces endometriosis-associated pain compared with leuprorelin in Japanese women: a phase 3, randomized, double-blind, noninferiority study. Fertil Steril. 2022 Mar;117(3):583-592.
5. Fukui Y, Hirota Y, Aikawa S, Ishizawa C, Iida R, Kaku T, et al. Uterine Receptivity is Reflected by LIF Expression in the Cervix. Reprod Sci. 2022 May;29(5):1457-1462.
6. Ono Y, Kawakita T, Yoshino O, Sato E, Kano K, Ohba M, et al. Sphingosine 1-Phosphate (S1P) in the Peritoneal Fluid Skews M2 Macrophage and Contributes to the Development of Endometriosis. Biomedicines. 2021 Oct 22;9(11):1519.
7. Ono M, Matsumoto K, Boku N, Fujii N, Tsuchida Y, Furui T, et al. Indications for fertility preservation not included in the 2017 Japan Society of Clinical Oncology Guideline for Fertility Preservation in Pediatric, Adolescent, and Young Adult Patients treated with gonadal toxicity, including benign diseases. Int J Clin Oncol. 2022 Feb;27(2):301-309.
8. Kusamoto A, Harada M, Azhary JMK, Kunitomi C, Nose E, Koike H, et al. Temporal relationship between alterations in the gut microbiome and the development of polycystic ovary syndrome-like phenotypes in prenatally androgenized female mice. FASEB J. 2021 Nov;35(11)
9. Satake E, Koga K, Takamura M, Izumi G, Elsherbini M, Taguchi A, et al. The roles of polymorphonuclear myeloid-derived suppressor cells in endometriosis. J Reprod Immunol. 2021 Nov;148:103371.
10. Shimamoto K, Hirano M, Wada-Hiraike O, Goto R, Osuga Y. Examining the association between menstrual symptoms and health-related quality of life among working women in Japan using the EQ-5D. BMC Womens Health. 2021 Sep 7;21(1): 325.
11. Fukui Y, Hirota Y, Saito-Fujita T, Aikawa S, Hiraoka T, Kaku T, et al. Uterine Epithelial LIF Receptors Contribute to Implantation Chamber Formation in Blastocyst Attachment. Endocrinology. 2021 Nov 1;162(11)
12. Harada M, Osuga Y. Does polycystic ovary syndrome independently affect oncologic and reproductive outcomes in patients with endometrial cancer receiving fertility-sparing treatment? J Gynecol Oncol. 2021 Sep;32(5):e80.
13. Osuga Y, Seki Y, Tanimoto M, Kusumoto T, Kudou K, Terakawa N. Relugolix, an oral gonadotropin-releasing hormone (GnRH) receptor antagonist, in women with endometriosis-associated pain: phase 2 safety and efficacy 24-week results. BMC Womens Health. 2021 Jun 21;21(1):250.
14. Osuga Y, Nakano Y, Yamauchi Y, Murakawa H. Phase III long-term study to evaluate the efficacy and safety of ulipristal acetate in Japanese patients with uterine fibroids. J Obstet Gynaecol Res. 2021 Sep;47(9):3269-3278.
15. Fukuoka K, Hirata T, Koga K, Morimoto C, Osuga Y. An Unusual Imaging Appearance of Peritoneal Endometriosis Presenting a Pelvic Multilocular Tumor. J Minim Invasive Gynecol. 2021 Sep;28(9):1561-1563.
16. Ota K, Tsutsumi O, Mitani T, Morimoto Y, Tanaka A, Osuga Y, et al. Reproductive medical providers' behaviors, considerations, and plans for fertility treatments during the COVID-19 pandemic in Japan: A nationwide web-based survey. Reprod Med Biol. 2021 Mar 22;20(2): 123-132.
17. Osuga Y, Nakano Y, Yamauchi Y, Takanashi M. Ulipristal acetate compared with leuprorelin acetate for Japanese women with symptomatic uterine fibroids: a phase III randomized controlled trial.Fertil Steril. 2021 Jul;116(1):189-197.
18. Harada M, Takahashi N, Azhary JM, Kunitomi C, Fujii T, Osuga Y. Endoplasmic reticulum stress: a key regulator of the follicular microenvironment in the ovary. Mol Hum Reprod. 2021 Jan 22; 27(1):
19. Makabe T, Koga K, Nagabukuro H, Asada M, Satake E, Taguchi A, et al.Use of selective PGE2 receptor antagonists on human endometriotic stromal cells and peritoneal macrophages. Mol Hum Reprod. 2021 Jan 22;27(1)

20. Kunitomi C, Harada M, Kusamoto A, Azhary JM, Nose E, Koike H, et al. Induction of aryl hydrocarbon receptor in granulosa cells by endoplasmic reticulum stress contributes to pathology of polycystic ovary syndrome. Mol Hum Reprod. 2021 Feb 27;27(3)
21. Ishihara O, Jwa SC, Kuwahara A, Katagiri Y, Kuwabara Y, Hamatani T, et al. Assisted reproductive technology in Japan: A summary report for 2018 by the Ethics Committee of the Japan Society of Obstetrics and Gynecology. Reprod Med Biol. 2020 Nov 20;20(1):3-12.
22. Ono Y, Yoshino O, Hiraoka T, Sato E, Furue A, Nawaz A, et al. CD206+ macrophage is an accelerator of endometriotic-like lesion via promoting angiogenesis in the endometriosis mouse model. Sci Rep. 2021 Jan 13;11(1):853
23. Akaeda S, Hirota Y, Fukui Y, Aikawa S, Shimizu-Hirota R, Kaku T, et al. Retinoblastoma protein promotes uterine epithelial cell cycle arrest and necroptosis for embryo invasion. EMBO Rep. 2021 Feb 3;22(2):
24. Hirata T, Koga K, Taniguchi F, Takazawa N, Honda R, Tanaka T, et al. National survey of bladder endometriosis cases in Japan. J Obstet Gynaecol Res. 2021 Apr;47(4):1451-1461.
25. Haraguchi H, Harada M, Kashimada K, Horikawa R, Sakakibara H, Shozu M, et al. National survey of primary amenorrhea and relevant conditions in Japan. J Obstet Gynaecol Res. 2021 Feb;47(2):774-777.
26. Halimi SA, Maeda D, Ushiku-Shinozaki A, Goto A, Oda K, Osuga Y, et al. Comprehensive immunohistochemical analysis of the gastrointestinal and Müllerian phenotypes of 139 ovarian mucinous cystadenomas. Hum Pathol. 2021 Mar;109:21-30.
27. Tsuchida Y, Harada M, Shoda H, Goto A, Suzuki N, Murashima A, et al. Fertility preservation in patients receiving gonadotoxic therapies for systemic autoimmune diseases in Japan. Mod Rheumatol. 2021 Sep;31(5):1004-1009
28. Okamoto S, Fujii N, Yoshioka N, Harada M, Tanimoto M, Maeda Y, et al. Nationwide survey of fertility preservation in patients with hematological malignancies in Japan. Int J Clin Oncol. 2021 Feb;26(2):438-442.
29. Osuga Y, Seki Y, Tanimoto M, Kusumoto T, Kudou K, Terakawa N. Relugolix, an oral gonadotropin-releasing hormone receptor antagonist, reduces endometriosis-associated pain in a dose-response manner: a randomized, double-blind, placebo-controlled study. Fertil Steril. 2021 Feb;115(2):397-405.
30. Sanada Y, Harada M, Kunitomi C, Kanatani M, Izumi G, Hirata T, et al. A Japanese nationwide survey on the cryopreservation of embryos, oocytes and ovarian tissue for cancer patients. J Obstet Gynaecol Res. 2019 Oct;45(10):2021-2028.

Department of Gynecologic Oncology

Associate Professor

Yutaka Osuga, Yasushi Hirota

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 sacralcolpopexy for pelvic organ prolapse
(4) 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 2021

(1) Kaneko S, Mitsuyama T, Shiraishi K, Ikawa N, Shozu K, Dozen A, Machino H, Asada K,

Komatsu M, Kukita A, Sone K, Yoshida H, Motoi N, Hayami S, Yoneoka Y, Kato T, Kohno T, Natsume T, Keudell GV, Saloura V, Yamaue H, Hamamoto R. Genome-Wide Chromatin Analysis of FFPE Tissues Using a Dual-Arm Robot with Clinical Potential. Cancers (Basel). 2021 Apr 28;13(9):2126. doi: 10.3390/cancers 13092126.

(2) Furusawa A, Takekuma M, Mori K, Usami T, Kondo E, Nishio S, Nishino K, Miyamoto Y, Yoshimura R, Watanabe M, Mikami M, Enomoto T. A randomized phase III trial of adjuvant chemotherapy versus concurrent chemo-radiotherapy for postoperative cervical cancer: Japanese Gynecologic Oncology Group study (JGOG1082). Int J Gynecol Cancer. 2021 Apr; 31(4):623-626. doi: 10.1136/ijgc-2020-002344.

(3) Ishikawa M, Shibata T, Iwata T, Nishio S, Takada T, Suzuki S, Horie K, Kudaka W, Kagabu M, Tanikawa M, Kitagawa R, Takekuma M, Kobayashi H, Yaegashi N; Japan Clinical Oncology Group. A randomized phase II/III trial of conventional paclitaxel and carboplatin with or without bevacizumab versus dose-dense paclitaxel and carboplatin with or without bevacizumab, in stage IVB, recurrent, or persistent cervical carcinoma (JCOG1311): Primary analysis. Gynecol Oncol. 2021 Aug;162(2):292-298. doi: 10.1016/j.ygyno.2021.05.007.

(4) Tanikawa M, Oda K. [□. Current Status and Issues of Genome Medicine in Gynecological Oncology]. Gan To Kagaku Ryoho. 2021 Feb;48(2):195-199.

(5) Konno Y, Asano H, Shikama A, Aoki D, Tanikawa M, Oki A, Horie K, Mitsuhashi A, Kikuchi A, Tokunaga H, Terao Y, Satoh T, Ushijima K, Ishikawa M, Yaegashi N, Watari H. Lymphadenectomy issues in endometrial cancer. J Gynecol Oncol. 2021 Mar;32(2):e25. doi: 10. 3802/jgo.2021.32.e25.

(6) Yamaguchi K, Matsumoto Y, Suzuki R, Nishida H, Omata D, Inaba H, Kukita A, Tanikawa M, Sone K, Oda K, Osuga Y, Maruyama K, Fujii T. Enhanced antitumor activity of combined lipid bubble ultrasound and anticancer drugs in gynecological cervical cancers. Cancer Sci. 2021 Jun;112(6):2493-2503. doi: 10.1111/cas. 14907.

(7) Sone K, Inoue F, Taguchi A, Hinata M, Ikemura M, Miyamoto Y, Michihiro T, Ohno T, Iriyama T, Mori-Uchino M, Tsuruga T, Mishima M, Osuga Y. A case of difficult-to-diagnose non-invasive papillary squamous cell carcinoma of the uterine cervix infected with human papilloma virus 6: A diagnostic pitfall. Clin Case Rep. 2021 Oct 4; 9(10):e04905. doi: 10.1002/ccr3.4905.

(8) Nara K, Taguchi A, Tojima Y, Miyamoto Y, Tanikawa M, Sone K, Mori M, Tsuruga T, Yamamoto T, Takenaka R, Takada T, Osuga Y, Suzuki H. History of whole pelvis plus para-aortic radiation is a risk factor associated with febrile neutropenia during chemotherapy for recurrent cervical cancer. Int J Clin Oncol. 2021 Sep;26(9):1759-1766. doi: 10.1007/s10147-021-01950-8.

(9) Sone K, Toyohara Y, Taguchi A, Miyamoto Y, Tanikawa M, Uchino-Mori M, Iriyama T, Tsuruga T, Osuga Y. Application of artificial intelligence in gynecologic malignancies: A review. J Obstet Gynaecol Res. 2021 Aug;47(8):2577-2585. doi: 10.1111/jog.14818.

(10) Ikeda Y, Adachi K, Tomio K, Eguchi-Kojima S, Tsuruga T, Uchino-Mori M, Taguchi A, Komatsu A, Nagamatsu T, Oda K, Kawana-Tachikawa A, Uemura Y, Igimi S, Osuga Y, Fujii T, Kawana K. A Placebo-Controlled, Double-Blind Randomized (Phase IIB) Trial of Oral Administration with HPV16 E7-Expressing *Lactobacillus*, GLBL101c, for the Treatment of Cervical Intraepithelial Neoplasia Grade 2 (CIN2). Vaccines (Basel). 2021 Apr 1; 9(4):329. doi: 10.3390/vaccines9040329

(11) Takahashi Y, Sone K, Noda K, Yoshida K, Toyohara Y, Kato K, Inoue F, Kukita A, Taguchi A, Nishida H, Miyamoto Y, Tanikawa M, Tsuruga T, Iriyama T, Nagasaka K, Matsumoto Y, Hirota Y, Hiraike-Wada O, Oda K, Maruyama M, Osuga Y, Fujii T. Automated system for diagnosing endometrial cancer by adopting deep-learning technology in hysteroscopy. PLoS One. 2021 Mar 31;16(3):e0248526. doi: 10.1371/journal.pone.0248526.

(12) Inoue F, Sone K, Toyohara Y, Takahashi Y, Kukita A, Hara A, Taguchi A, Tanikawa M, Tsuruga T, Osuga Y. Targeting Epigenetic Regulators for Endometrial Cancer Therapy: Its Molecular Biology and Potential Clinical Applications. Int J Mol Sci. 2021 Feb 25;22(5): 2305. doi: 10.3390/ijms22052305.
(13) Taguchi A, Nakajima Y, Furusawa A, Yoshino Y, Takao M, Kashiyama T, Kino N, Yasugi T. High neutrophil-to-lymphocyte ratio is a predictor of short-term survival for patients with recurrent cervical cancer after radiation-based therapy. J Obstet Gynaecol Res. 2021 May;47(5):1862-1870. doi: 10.1111/jog.14712.
(14) Kawata A, Taguchi A, Baba S, Miyamoto Y, Tanikawa M, Sone K, Tsuruga T, Mori M, Oda K, Kawana K, Osuga Y, Fujii T. A low preoperative albumin-to-globulin ratio is a negative prognostic factor in patients with surgically treated cervical cancer. Int J Clin Oncol. 2021 May;26(5):980-985. doi: 10.1007/ s10147-021-01861-8.

Department of Perinatal Medicine

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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 2021

1. Matsui H, Iriyama T, Sayama S, Inaoka N, Suzuki K, Yoshikawa M, Ichinose M, Sone K, Kumasawa K, Nagamatsu T, Fujisawa T, Naguro I, Ichijo H, Fujii T, Osuga Y. Elevated placental

histone H3K4 methylation via upregulated histone methyltransferases SETD1A and SMYD3 in preeclampsia and its possible involvement in hypoxia-induced pathophysiological process. Placenta. 2021 Nov; 115:60-69.

2. Oda H, Nagamatsu T, Cabral H, Miyazaki T, Iriyama T, Kawana K, Fujii T, Osuga Y. Thrombomodulin promotes placental function by up-regulating placental growth factor via inhibition of high-mobility-group box 1 and hypoxia-inducible factor 1α. Placenta. 2021 Aug; 111:1-9.
3. Toshimitsu M, Iriyama T, Sayama S, Suzuki K, Kakiuchi S, Ichinose M, Seyama T, Sone K, Kumasawa K, Nagamatsu T, Fujii T, Osuga Y. A Fetus with Imperforate Anus Developing Pulmonary Hypoplasia Triggered by Transient Urethral Obstruction. Case Rep Obstet Gynecol. 2021 May: 9950578.
4. Oda H, Nagamatsu T, Schust DJ, Cabral H, Miyazaki T, Iriyama T, Kawana K, Osuga Y, Fujii T. Recombinant Thrombomodulin Attenuates Preeclamptic Symptoms by Inhibiting High-Mobility Group Box 1 in Mice. Endocrinology. 2021 Apr 1;162(4)
5. Akiba N, Iriyama T, Nakayama T, Seyama T, Sayama S, Kumasawa K, Komatsu A, Yabe S, Nagamatsu T, Osuga Y, Fujii T. Ultrasonographic vascularity assessment for predicting future severe hemorrhage in retained products of conception after second-trimester abortion.J Matern Fetal Neonatal Med. 2021 Feb; 34(4):562-568.
6. Shitara R, Iriyama T, Sayama S, Takeda N, Nagamatsu T, Osuga Y, Fujii T. Postpartum Stanford type B aortic dissection in a woman with Loeys-Dietz syndrome who underwent a prophylactic aortic root replacement before conception: A case report. Taiwan J Obstet Gynecol. 2021 Jan;60(1):145-147.
7. Ohkuchi A, Saito S, Yamamoto T, Minakami H, Masuyama H, Kumasawa K, Yoshimatsu J, Nagamatsu T, Dietl A, Grill S, Hund M. Short-term prediction of preeclampsia using the sFlt-1/PlGF ratio: a subanalysis of pregnant Japanese women from the PROGNOSIS Asia study. Hypertens Res. 2021 Jul;44(7):813-821.
8. Azuma K, Okubo A, Suzuki T, Igarashi N, Nomura Y, Soga H, Murata H, Fujino R, Ogawa A, Matsui H, Nagamatsu T, Iriyama T, Asaoka R, Inoue T, Maruyama-Inoue M, Kadonosono K, Obata R. Assessment of the choroidal structure in pregnant women in the first trimester. Sci Rep. 2021 Feb 25;11(1):4629.
9. Shibuya M, Matsui H, Sasagawa T, Nagamatsu T. A simple detection method for the serum sFLT1 protein in preeclampsia. Sci Rep. 2021 Oct 18; 11(1):20613.
10. Shindo R, Aoki S, Misumi T, Nakanishi S, Umazume T, Nagamatsu T, Masuyama H, Itakura A, Ikeda T; Japan Society of Obstetrics and Gynecology Perinatal Committee. Spontaneous labor curve based on a retrospective multi-center study in Japan. J Obstet Gynaecol Res. 2021 Dec; 47(12):4263-4269.
11. Nomoto M, Kotani T, Miki R, Ushida T, Imai K, Iitani Y, Tano S, Wang J, Moriyama Y, Kobayashi T, Mimura N, Iriyama T, Kikkawa F, Kajiyama H. Upregulation of ENDOU in cytotrophoblasts from placenta complicated with preeclampsia and fetal growth restriction. J Clin Biochem Nutr. 2021 Nov;69(3):280-285.
12. Ishigami D, Koizumi S, Ishikawa O, Toshimitsu M, Iriyama T, Miyawaki S, Saito N. Embolization of dural arteriovenous fistula during twin pregnancy - A case report and literature review. Interv Neuroradiol. 2021 Oct; 27(5):658-662.
13. Suzuki T, Inoue T, Igarashi N, Agata C, Okubo A, Nagamatsu T, Iriyama T, Maruyama-Inoue M, Yanagi Y, Kadonosono K, Asaoka R, Azuma K, Obata R. Association between serum soluble fms-like tyrosine kinase-1 and the central choroidal thickness during pregnancy: a prospective study. BMJ Open Ophthalmol. 2021 Nov 5;6(1):e000888.
14. Sasagawa T, Nagamatsu T, Yanagisawa M, Fujii T, Shibuya M. Hypoxia-inducible factor-1β is essential for upregulation of the hypoxia-induced FLT1 gene in placental trophoblasts. Mol Hum Reprod. 2021 Nov 27;27(12)
15. Suzuki T, Inoue T, Igarashi N, Agata C, Okubo A, Nagamatsu T, Iriyama T, Maruyama-Inoue M, Yanagi Y, Kadonosono K, Asaoka R, Azuma K,

Obata R. Association between serum soluble fms-like tyrosine kinase-1 and the central choroidal thickness during pregnancy: a prospective study. BMJ Open Ophthalmol. 2021 Nov 5;6(1):e000888.

16. Samejima T, Yamashita T, Takeda Y, Adachi T. Identifying the associated factors with onset of preterm PROM compared with term PROM - A retrospective cross-sectional study. Taiwan J Obstet Gynecol. 2021 Jul;60(4):653-657.
17. Samejima T, Yamashita T, Takeda Y, Adachi T. Low antithrombin levels accompanied by high urine protein/creatinine ratios are predictive of acute kidney injury among CS patients with preeclampsia. J Matern Fetal Neonatal Med. 2021 May;34(10):1550-1556.
18. Ichinose M, Suzuki N, Wang T, Kobayashi H, Vrbanac L, Ng JQ, Wright JA, Lannagan TRM, Gieniec KA, Lewis M, Ando R, Enomoto A, Koblar S, Thomas P, Worthley DL, Woods SL: The BMP antagonist gremlin1 contributes to the development of cortical excitatory neurons, motor balance and fear responses. Development. 2021 Jul 15;148(14)
19. Ichinose M, Suzuki N, Wang T, Wright JA, Lannagan TRM, Vrbanac L, Kobayashi H, Gieniec KA, Ng JQ, Hayakawa Y, García-Gallastegui P, Monsalve EM, Bauer SR, Laborda J, García-Ramírez JJ, Ibarretxe G, Worthley DL, Woods SL. Stromal DLK1 promotes proliferation and inhibits differentiation of the intestinal epithelium during development. Am J Physiol Gastrointest Liver Physiol. 2021 Apr 1;320(4): G506-G520.
20. Ichinose M, Suzuki N, Wang T, Wright JA, Lannagan TRM, Vrbanac L, Kobayashi H, Gieniec K, Ng JQ, Ihara S, Mavrangelos C, Hayakawa Y, Hughes P, Worthley DL, Woods SL. Delineating proinflammatory micro-environmental signals by ex vivo modeling of the immature intestinal stroma. Sci Rep Mar 30; 11(1):7200.

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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 annualy. 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 gonadotoropins.
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 approches, we also manage patients complaining primary/secondary amenorrhea, infertility, dysmenorrhea, heavy menstrual bleeding, and climactirium. Osteoporosis in their 10's to 20's and perimenopausal age could be a heavy burden for patinets 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 2021

1. Katagiri Y, Jwa SC, Kuwahara A, Iwasa T, Ono M, Kato K, et al. Assisted reproductive technology in Japan: A summary report for 2019 by the Ethics Committee of the Japan Society of Obstetrics and Gynecology. Reprod Med Biol. 2021 Dec 14;21(1):e12434.
2. Kanda R, Miyagawa Y, Wada-Hiraike O, Hiraike H, Nagasaka K, Ryo E, et al. Ulipristal acetate simultaneously provokes antiproliferative and proinflammatory responses in endometrial cancer cells. Heliyon. 2021 Dec 29;8(1).
3. Kuji S, Harada M, Yoshioka N, Kajiyama H, Satoh T, Mikami M, et al. Survival and reproductive outcomes after fertility-sparing surgery performed for borderline epithelial

ovarian tumor in Japanese adolescents and young adults: Results of a retrospective nationwide study. J Obstet Gynaecol Res. 2022 Mar;48(3): 806-816.

4. Harada T, Osuga Y, Suzuki Y, Fujisawa M, Fukui M, Kitawaki J. Relugolix, an oral gonadotropin-releasing hormone receptor antagonist, reduces endometriosis-associated pain compared with leuprorelin in Japanese women: a phase 3, randomized, double-blind, noninferiority study. Fertil Steril. 2022 Mar;117(3):583-592.
5. Fukui Y, Hirota Y, Aikawa S, Ishizawa C, Iida R, Kaku T, et al. Uterine Receptivity is Reflected by LIF Expression in the Cervix. Reprod Sci. 2022 May;29(5):1457-1462.
6. Ono Y, Kawakita T, Yoshino O, Sato E, Kano K, Ohba M, et al. Sphingosine 1-Phosphate (S1P) in the Peritoneal Fluid Skews M2 Macrophage and Contributes to the Development of Endometriosis. Biomedicines. 2021 Oct 22;9(11):1519.
7. Ono M, Matsumoto K, Boku N, Fujii N, Tsuchida Y, Furui T, et al. Indications for fertility preservation not included in the 2017 Japan Society of Clinical Oncology Guideline for Fertility Preservation in Pediatric, Adolescent, and Young Adult Patients treated with gonadal toxicity, including benign diseases. Int J Clin Oncol. 2022 Feb;27(2):301-309.
8. Kusamoto A, Harada M, Azhary JMK, Kunitomi C, Nose E, Koike H, et al. Temporal relationship between alterations in the gut microbiome and the development of polycystic ovary syndrome-like phenotypes in prenatally androgenized female mice. FASEB J. 2021 Nov;35(11)
9. Satake E, Koga K, Takamura M, Izumi G, Elsherbini M, Taguchi A, et al. The roles of polymorphonuclear myeloid-derived suppressor cells in endometriosis. J Reprod Immunol. 2021 Nov;148:103371.
10. Shimamoto K, Hirano M, Wada-Hiraike O, Goto R, Osuga Y. Examining the association between menstrual symptoms and health-related quality of life among working women in Japan using the EQ-5D. BMC Womens Health. 2021 Sep 7;21(1): 325.
11. Fukui Y, Hirota Y, Saito-Fujita T, Aikawa S, Hiraoka T, Kaku T, et al. Uterine Epithelial LIF Receptors Contribute to Implantation Chamber Formation in Blastocyst Attachment. Endocrinology. 2021 Nov 1;162(11)
12. Harada M, Osuga Y. Does polycystic ovary syndrome independently affect oncologic and reproductive outcomes in patients with endometrial cancer receiving fertility-sparing treatment? J Gynecol Oncol. 2021 Sep;32(5):e80.
13. Osuga Y, Seki Y, Tanimoto M, Kusumoto T, Kudou K, Terakawa N. Relugolix, an oral gonadotropin-releasing hormone (GnRH) receptor antagonist, in women with endometriosis-associated pain: phase 2 safety and efficacy 24-week results. BMC Womens Health. 2021 Jun 21;21(1):250.
14. Osuga Y, Nakano Y, Yamauchi Y, Murakawa H. Phase III long-term study to evaluate the efficacy and safety of ulipristal acetate in Japanese patients with uterine fibroids. J Obstet Gynaecol Res. 2021 Sep;47(9):3269-3278.
15. Fukuoka K, Hirata T, Koga K, Morimoto C, Osuga Y. An Unusual Imaging Appearance of Peritoneal Endometriosis Presenting a Pelvic Multilocular Tumor. J Minim Invasive Gynecol. 2021 Sep;28(9):1561-1563.
16. Ota K, Tsutsumi O, Mitani T, Morimoto Y, Tanaka A, Osuga Y, et al. Reproductive medical providers' behaviors, considerations, and plans for fertility treatments during the COVID-19 pandemic in Japan: A nationwide web-based survey. Reprod Med Biol. 2021 Mar 22;20(2): 123-132.
17. Osuga Y, Nakano Y, Yamauchi Y, Takanashi M. Ulipristal acetate compared with leuprorelin acetate for Japanese women with symptomatic uterine fibroids: a phase III randomized controlled trial.Fertil Steril. 2021 Jul;116(1):189-197.
18. Harada M, Takahashi N, Azhary JM, Kunitomi C, Fujii T, Osuga Y. Endoplasmic reticulum stress: a key regulator of the follicular microenvironment in the ovary. Mol Hum Reprod. 2021 Jan 22; 27(1):
19. Makabe T, Koga K, Nagabukuro H, Asada M, Satake E, Taguchi A, et al.Use of selective PGE2 receptor antagonists on human endometriotic

stromal cells and peritoneal macrophages. Mol Hum Reprod. 2021 Jan 22;27(1)
20. Kunitomi C, Harada M, Kusamoto A, Azhary JM, Nose E, Koike H, et al. Induction of aryl hydrocarbon receptor in granulosa cells by endoplasmic reticulum stress contributes to pathology of polycystic ovary syndrome. Mol Hum Reprod. 2021 Feb 27;27(3)
21. Ishihara O, Jwa SC, Kuwahara A, Katagiri Y, Kuwabara Y, Hamatani T, et al. Assisted reproductive technology in Japan: A summary report for 2018 by the Ethics Committee of the Japan Society of Obstetrics and Gynecology. Reprod Med Biol. 2020 Nov 20;20(1):3-12.
22. Ono Y, Yoshino O, Hiraoka T, Sato E, Furue A, Nawaz A, et al. CD206+ macrophage is an accelerator of endometriotic-like lesion via promoting angiogenesis in the endometriosis mouse model. Sci Rep. 2021 Jan 13;11(1):853
23. Akaeda S, Hirota Y, Fukui Y, Aikawa S, Shimizu-Hirota R, Kaku T, et al. Retinoblastoma protein promotes uterine epithelial cell cycle arrest and necroptosis for embryo invasion. EMBO Rep. 2021 Feb 3;22(2):
24. Hirata T, Koga K, Taniguchi F, Takazawa N, Honda R, Tanaka T, et al. National survey of bladder endometriosis cases in Japan. J Obstet Gynaecol Res. 2021 Apr;47(4):1451-1461.
25. Haraguchi H, Harada M, Kashimada K, Horikawa R, Sakakibara H, Shozu M, et al. National survey of primary amenorrhea and relevant conditions in Japan. J Obstet Gynaecol Res. 2021 Feb;47(2):774-777.
26. Halimi SA, Maeda D, Ushiku-Shinozaki A, Goto A, Oda K, Osuga Y, et al. Comprehensive immunohistochemical analysis of the gastro-intestinal and Müllerian phenotypes of 139 ovarian mucinous cystadenomas. Hum Pathol. 2021 Mar;109:21-30.
27. Tsuchida Y, Harada M, Shoda H, Goto A, Suzuki N, Murashima A, et al. Fertility preservation in patients receiving gonadotoxic therapies for systemic autoimmune diseases in Japan. Mod Rheumatol. 2021 Sep;31(5):1004-1009
28. Okamoto S, Fujii N, Yoshioka N, Harada M, Tanimoto M, Maeda Y, et al. Nationwide survey of fertility preservation in patients with hematological malignancies in Japan. Int J Clin Oncol. 2021 Feb;26(2):438-442.
29. Osuga Y, Seki Y, Tanimoto M, Kusumoto T, Kudou K, Terakawa N. Relugolix, an oral gonadotropin-releasing hormone receptor antagonist, reduces endometriosis-associated pain in a dose-response manner: a randomized, double-blind, placebo-controlled study. Fertil Steril. 2021 Feb;115(2):397-405.
30. Sanada Y, Harada M, Kunitomi C, Kanatani M, Izumi G, Hirata T, et al. A Japanese nationwide survey on the cryopreservation of embryos, oocytes and ovarian tissue for cancer patients. J Obstet Gynaecol Res. 2019 Oct;45(10):2021-2028.

Reproductive, Developmental and Aging Sciences

2. Pediatric Sciences

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(As of March 31, 2022)

Homepage http://square.umin.ac.jp/ped/

Introduction and Organization

The former Department of Pediatrics developed into the Department of Pediatrics and Department of Developmental Pediatrics, which comprise subgroups of the Group of Reproductive, Developmental and Aging Medicines, Graduate School of Medicine, The University of Tokyo.

Our staff consists of 2 professors, 2 associate professors, 3 lecturers, 3 project lecturers, 34 research associates on March 31, 2022.

The outpatient clinic of our department is on the second floor of the outpatient clinic building. We treat patients at the Pediatric Medical Center in the inpatient building. The offices are on the second and third floors of the East Research Building.

Our laboratories are also located on the seventh floor of the Clinical Research Building Center and on the second and third floors of the East Research Building.

Clinical activities

The outpatient pediatric clinics cover a large part of pediatric disorders; hematology / oncology, cardiology, neurology, nephrology, endocrinology, and neonatology. Additionally, patients with genetics, pulmonology, and allergology / immunology are followed by part-time physicians who cover each field.

In cooperation with Department of Family Nursing, we have been managing two clinics for supporting the patients by nurses and other health care professionals, “Post-transplantation follow-up clinic” and “Transitional care clinic”. Both clinics offer the patients opportunities to discuss their diseases without their parents, aiming for attaining self-management regarding their disease and health care.

We also follows up with patients after discharge from the hospital in an outpatient clinic and provides medical care that meets the needs of patients and their families based on collaboration with local medical institutions.

We have specialized clinics that cover all fields of pediatric disorders. Children or neonates stay in the Pediatric Medical Center and receive appropriate treatments. Since June, 2019, we have increased activity of intensive care and developed the section of Pediatric and Perinatal Intensive Care including neonatal intensive care unit (NICU) and the pediatric intensive care unit (PICU). PICU is one of the tertiary centers of pediatric emergency covering the eastern part of Tokyo. There are 12 beds in the PICU and our institution is going to fulfill the designation as a children's hospital affiliated with the university hospital. The PICU provides advanced monitoring and comprehensive care for children with critical illness or injury, as well as those with complex medical needs. Our highly skilled team has specialized training and equipment to quickly assess and treat children with serious or life-threatening medical issues. Our PICUs provide critical care to any child who needs it. We care for children who face a wide range of severe and complex medical conditions, including severe infections, single or multi-organ system failure, traumatic injuries, such as burns and injuries to the head, chest and abdomen, respiratory failure and severe asthma attacks, recovery from complex orthopedic, neurologic and general surgeries, as well as organ transplants.

There are 21 beds in the NICU and 36 beds in the growing care unit (GCU). In the NICU/GCU, we are taking care of many high-risk infants which comprise small premature babies weighing less than 500g and newborns with congenital disorders requiring invasive interventions (e.g. congenital heart disease, gastrointestinal malformation). Our team have many well-trained staffs, and we provide high-quality specialized medical care as one of the representative perinatal centers of Tokyo, by collaborating with obstetricians, pediatric cardiologists, cardiac surgeons, pediatric surgeons, ophthalmologists, neurosurgeons, etc. Moreover, we facilitate family-centered care by collaborating with co-medical staffs.

In the general ward of the Pediatric Medical Center, we treat a variety of patients with diseases, such as hematological/oncological disorders, cardiac disorders, neuromuscular disorders, immunological/allergic disorders, renal and urinary tract diseases, endocrinological disorders, metabolic disorders, and psychosomatic diseases are admitted to the wards. In addition, we provide comprehensive medical care for patients with systemic diseases or biopsychosocial problems in cooperation with related departments. The hospital was also accredited as a provider of chimeric antigen receptor T-cell therapy.

At the Department of Pediatrics, we pay for all treatment; McDonald House housing for families with options for larger accommodations with low-price staying. Our on-site school allows patients to keep up with their school program back home. We offer numerous other services for our families, including psychosocial help for caregivers and siblings coping with a child’s diseases diagnosis; child life specialists, translation help for those who do not speak Japanese

as a first language, Niko-niko Volunteer and much more.

Many patients need to stay longer in the hospital. We provide an official in-hospital school 'Kodama Gakkyu' where patients receive education and have the opportunity to communicate with other patients and their family members. Members of the 'Niko-niko Volunteer', an official volunteer group in the hospital, visit the pediatric ward every weekday to play with patients and help their mothers, providing enormous comfort to both patients and their mothers. Various activities are scheduled for patients in the hospital. All the residents, fellows and nurses participate in these activities. We have two child care specialists in the pediatric ward.

Teaching activities

Systematic lectures about general and highly specialized pediatrics are provided for the second-grade students with staff members and visiting lecturers. The third-grade students receive two weeks of practical training in hospital wards (M3 clinical clerkship). During the bedside training period, students are as-signed to each clinical team and are in charge of in-patients, taking their medical history, examining them, recording their hospital records, and observing various examinations. During the period, specific pediatric lectures are provided including about pediatric neurology, nephrology, transfusion, endocrinology, neonatology, hematology/oncology, emergency resuscitation, and so on. The practice will be interactive, combining face-to-face and online under current social situation. We also offer an elective clinical clerkship course for those who are especially interested in pediatrics in their fourth grade. Students are assigned to a ward on a month-to-month basis, allowing them to experience highly specialized training tailored to their individual needs. Observing the outpatient clinic and learning the normal development of children are another goal for the fourth-grade students (M4 clinical clerkship). On the last day of each clerkship, the professor evaluates the students' achievements. We also provide a variety of online learning contents through the educational website of department of pe-diatrics (https://sites.google.com/d/1EXrB_7WZBlLzw9SooY3a4bm2MnNe_PbJ/p/1h3YBWtv_FcpVQy98dkUBfN1-4bdlkIRg/edit).

Research activities

Our departments have the following research groups: nephrology, hematology/oncology, neurology, cardiology, endocrinology/metabolism, immunology/ allergy, and neonatology. We also have multi-disciplinary research groups and laboratories such as cell biology, genetic molecular biology, and epidemiology. The main research topics during the last year are listed below.

Hematology/Oncology group:

Our division has performed whole-genome sequencing (WGS), whole-exome sequencing (WES) and RNA-Sequencing with more than 500 pediatric cancer patients to investigate the underlying mechanism of pediatric hematologic diseases and cancer such as leukemia, rhabdomyosarcoma and neuroblastoma.

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 also analyze the pathogenic mechanism of nail-patella syndrome.

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:

Using mouse models of genetic disorders (e.g., tuberous sclerosis) and environmental burdens (e.g.,

in utero exposure to valproic acid), the pathogenetic mechanism of neuro-developmental disorders is investigated. A clinical trial of valganciclovir, an antiviral drug for cytomegalovirus infection has been conducted for infants with congenital cytomegalovirus infection, which showed therapeutic efficacy of valganciclovir for recovering hearing difficulty.

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 conducts biological response research using physiological data of critical illnesses, such as heart rate variability analysis, quantification of neural reflexes, evaluation of cerebral blood flow regulation, and pulse wave analysis, as well as medical safety research using DWH, development of digital fundoscopes, and echo imaging research of postoperative hemodynamics.

Selected References

1. Kotajima-Murakami H, Hagihara H, Sato A, Hagino Y, Tanaka M, Katoh Y, Nishito Y, Takamatsu Y, Uchino S, Miyakawa T, Ikeda K. Exposure to GABAA Receptor Antagonist Picrotoxin in Pregnant Mice Causes Autism-Like Behaviors and Aberrant Gene Expression in Offspring. Front Psychiatry. 2022 Feb 3;13: 821354. doi: 10.3389/fpsyt.2022.821354.
2. Morioka I, Kakei Y, Omori T, Nozu K, Fujioka K, Takahashi N, Yoshikawa T, Moriuchi H, Ito Y, Oka A; Japanese Congenital 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.
3. Yoshida M, Nakabayashi K, Yang W, Sato-Otsubo A, Tsujimoto SI, Ogata-Kawata H, Kawai T, Ishiwata K, Sakamoto M, Okamura K, Yoshida K, Shirai R, Osumi T, Moriyama T, Nishii R, Takahashi H, Kiyotani C, Shioda Y, Terashima K, Ishimaru S, Yuza Y, Takagi M, Arakawa Y, Kinoshita A, Hino M, Imamura T, Hasegawa D, Nakazawa Y, Okuya M, Kakuda H, Takasugi N, Inoue A, Ohki K, Yoshioka T, Ito S, Tomizawa D, Koh K, Matsumoto K, Sanada M, Kiyokawa N, Ohara A, Ogawa S, Manabe A, Niwa A, Hata K, Yang JJ, Kato M. NUDT15 variants confer high incidence of second malignancies in children with acute lymphoblastic leukemia. Blood Adv 2021 Dec 14;5(23):5420-5428.
4. Nishii R, Mizuno T, Rehling D, Smith C, Clark BL, Zhao X, Brown SA, Smart B, Moriyama T, Yamada Y, Ichinohe T, Onizuka M, Atsuta Y, Yang L, Yang W, Thomas PG, Stenmark P, Kato M, Yang JJ. NUDT15 polymorphism influences the metabolism and therapeutic effects of acyclovir and ganciclovir. Nat Commun. 2021 Jul 7;12(1):4181.
5. Takeda N, Inuzuka R, Yagi H, Morita H, Ando M, Yamauchi H, Taniguchi Y, Porto KJ, Kanaya T, Ishiura H, Mitsui J, Tsuji S, Toda T, Ono M, Komuro I. Clinical Impact of Copy Number Variation on the Genetic Diagnosis of Syndromic Aortopathies. Circ Genom Precis Med. 2021 Aug;14(4)
6. Nii M, Inuzuka R, Inai K, Shimada E, Shinohara T, Kogiso T, Ono H, Ootsuki S, Kurita Y, Takeda A, Hirono K, Takei K, Yasukochi S, Yoshikawa T, Furutani Y, Shinozaki T, Matsuyama Y, Senzaki H, Tokushige K, Nakanishi T. Incidence and Expected Probability of Liver Cirrhosis and Hepatocellular Carcinoma After Fontan Operation. Circulation. 2021 Dec 21;144(25):2043-2045.
7. Tomita H, Kim SH, Inuzuka R, Matsui H, Tachimori H, Kobayashi T, Kato A, Fujii T, Haishima Y, Okamoto Y, Sakoda H. Stent Implantation for Congenital Heart Diseases in Japan - Comprehensive Analysis From the Japanese Society of Congenital Interventional Cardiology Registry. Circ J. 2021 Aug 25;85(9):

1517-1524.
8. Shitara Y, Kakiuchi S, Mukai T, Kashima K, Kato M, Takahashi N. Case Report: Treatment of Extremely Preterm Infants With Birthweight Below 300 g: Case Series. Front Pediatr. 2021 Dec 6;9:758683.
9. Shitara Y, Watanabe E, Takahashi N. A term infant with fetal giant meconium hydrocele caused by meconium peritonitis. Pediatr Neonatol. 2021 Jul;62(4):445-446.

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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 pillers 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) Fujishiro J, Fujiogi M, Hirahara N, Terui K, Okamoto T, Watanabe E, Ishimaru T, Miyata H: Abdominal Drainage at Appendectomy for Complicated Appendicitis in Children:

A Propensity-matched Comparative Study. Ann Surg 274: e599-e604, 2021. doi: 10.1097/SLA.0000000000003804.

(2) Sunouchi T, Watanabe Y, Tomonaga K, Watanabe E, Ichijo C, Hoshino N, Suzuki K, Fujishiro J: Optimal treatment of pneumothorax in adolescents with Marfan syndrome. J Pediatr Surg 56: 1103-1106, 2021. doi: 10.1016/j.jpedsurg.2021.03.021.

(3) Suzuki K, Komura M, Obana K, Komura H, Inaki R, Fujishiro J, Suzuki K, Nakayama Y: A new method of primary engineering of esophagus using orthotopic in-body tissue architecture. J Pediatr Surg 56: 1186-1191, 2021. doi: 10.1016/j.jpedsurg.2021.03.025.

(4) Fujishiro J, Watanabe E, Hirahara N, Terui K, Tomita H, Ishimaru T, Miyata H: Laparoscopic Versus Open Appendectomy for Acute Appendicitis in Children: a Nationwide Retrospective Study on Postoperative Outcomes. J Gastrointest Surg 25: 1036-1044, 2021. doi: 10.1007/s11605-020-04544-3.

(5) Konishi KI, Mizuochi T, Takei H, Yasuda R, Sakaguchi H, Ishihara J, Takaki Y, Kinoshita M, Hashizume N, Fukahori S, Shoji H, Miyano G, Yoshimaru K, Matsuura T, Sanada Y, Tainaka T, Uchida H, Kubo Y, Tanaka H, Sasaki H, Murai T, Fujishiro J, Yamashita Y, Nio M, Nittono H, Kimura A: A Japanese prospective multicenter study of urinary oxysterols in biliary atresia. Sci Rep 11: 4986, 2021. Doi: 10.1038/s41598-021-84445-w.

(6) Suzuki K, Fujishiro J, Ichijo C, Watanabe E, Tomonaga K, Sunouchi T, Watanabe Y: Prophylactic innominate artery transection to prevent tracheoinnominate artery fistula: a retrospective review of single institution experiences. Pediatr Surg Int 37: 267-273, 2021. doi: 10.1007/s00383-020-04792-z.

(7) Shinya Takazawa, Akira Nishi, Tetsuya Ishimaru, Masataka Takahashi, Tomohiro Sunouchi, Kenta Kikuchi, Ryota Koyama: Face and construct validity assessment of training models for intestinal anastomosis in low-birth-weight infants. Pediatr Surg Int 37: 1765-1772, 2021. doi: 10.1007/s00383-021-04991-2.

(8) Aiyoshi T, Masumoto K, Tanaka N, Sasaki T, Chiba F, Ono K, Jimbo T, Urita Y, Shinkai T, Takayasu H, Hitomi S: Optimal First-Line Antibiotic Treatment for Pediatric Complicated Appendicitis Based on Peritoneal Fluid Culture. Pediatr Gastroenterol Hepatol Nutr 24: 510-517, 2021

(9) Kanako Omata, Noriki Okada, Go Miyahara, Yuta Hirata, Yukihiro Sanada, Yasuharu Onishi, Shinya Fukuda, Hideki Kumagai, Alan K Lefor, Yasunaru Sakuma, Naohiro Sata: Peliosis Hepatis in a Child with X-Linked Myotubular Myopathy Treated with Living-Donor Liver Transplant: A Case Report. Transplantation Proceeding 53: 1317-1321, 2021

(10) Ogawa S, Nishihara M, Nakanishi T, Maeda T, Hirota S: A rare case of extraluminally pedunculated gastrointestinal stromal tumor with postoperative metastasis to pancreas. J Surg Case Rep 2021: rjab422, 2021

(11) C Ichijo, S Takami, K Suzuki, J Fujishiro, M Watanabe: Retroperitoneal lymphatic malformation causing scrotal swelling a useful diagnostic work-up with two-phase MRI to differentiate from scrotal lymphatic malformation or abdomino-scrotal hydrocele. JPS case reports, 64, 2021, 101701

(12) Yamada K, Ishikawa T, Ohno E, Iida T, Suzuki H, Uetsuki K, Yashika J, Yoshikawa, Takami H, Inokawa Y, Uchida H, Kawashima H, Fujishiro M: Double common bile duct associated with pancreaticobiliary maljunction. Nagoya Journal of Medical Science 83: 655-661, 2021

(13) Amano H, Shirota C, Tainaka T, Sumida W, Yokota K, Makita S Takimoto A, Tanaka Y, Hinoki A, Kawashima H, Uchida H: Late postoperetive complication of congenital biliary dilatation in pediatric patients: single-center experience of managing complications for over 20 years. Surgery Today 37: 1675-1682, 2021

(14) Yohei Sanmoto, Tetsuya Ishimaru, Kentaro Hyashi, Osamu Tomita, Koichi Oshima, Atsuko Nakazawa, Katuyoshi Koh, Hiroshi Kawashima: Scrlerosing angiomatoid nodukar transformetion in a child. Juounal of Peditric Surgery Case Report. (2021). Doi:https//doi,org/10.1016/j.epsc.2021.101836

(15) Ishimaru T, Kawashima H, Hayashi K, Omata K,

Sanmoto Y, Inoue M: Laparoscopically assisted anorectoplasty-Surgical procedures and outcomes: A literature review. Asian J Endosc Surg 14: 335-345, 2021

(16) Ishimaru T, Kawashima H, Hayashi K, Oiki H, Omata K, Sanmoto Y, Inoue M: A Comparison of Sexual Function in Male Patients with Anorectal Malformations Between the Conventional and Laparoscopic Approaches. J Laparoendosc Adv Surg Tech A 31: 1420-1423, 2021

(17) M Takahashi, Y Kanamori, T Kobayashi, M Kobayashi, K Tsukamoto, S Yamagishi, R Furugane, M Kutsukake, T Mori, M Kano, A Yoneda, Y Ito, A Fujino: Triple duodenal obstruction" complicated with intestinal malrotation and several cardiovascular malformations. JPS case reports. 2021; 75: 102078.

(18) Sakamoto T, Fujiogi M, Matsui H, Fushimi K, Yasunaga H: Comparing Perioperative Mortality and Morbidity of Minimally Invasive Esophagectomy Versus Open Esophagectomy for Esophageal Cancer: A Nationwide Retrospective Analysis. Ann Surg 274: 324-330, 2021. doi: 10.1097/SLA.0000000000003500.

(19) Patregnani JT*, Fujiogi M*, Camargo CA, Brooks BA, Hoptay CE, Mansbach JM, Teach SJ, Freishtat RJ, Hasegawa K: Serum Soluble Receptor for Advanced Glycation End Products in Infants With Bronchiolitis: Associations With Acute Severity and Recurrent Wheeze. Clin Infect Dis 73: e2665-e2672, 2021. doi: 10.1093/cid/ciaa1700. * J. T. P. and M. F. contributed equally to this work

(20) Fujiogi M, Camargo CA Jr, Raita Y, Zhu Z, Celedón JC, Mansbach JM, Spergel JM, Hasegawa K: Integrated associations of nasopharyngeal and serum metabolome with bronchiolitis severity and asthma: A multicenter prospective cohort study. Pediatr Allergy Immunol 32: 905-916, 2021. doi: 10.1111/pai.13466.

(21) Fujiogi M, Camargo CA Jr, Raita Y, Toivonen L, Freishtat RJ, Mansbach JM, Piedra PA, Hasegawa K: Association of endemic coronaviruses with nasopharyngeal metabolome and microbiota among infants with severe bronchiolitis: a prospective multicenter study. Pediatr Res 89: 1594-1597, 2021. doi: 10.1038/s41390-020-01154-2.

(22) Hayashi K, Ishimaru T, Lee J, Hirai S, Ooke T, Hosokawa T, Omata K, Sanmoto Y, Kakihara T, Kawashima H: Identification of Appendicitis Using Ultrasound with the Aid of Machine Learning. J Laparoendosc Adv Surg Tech A. 2021 Nov 5. doi: 10.1089/lap.2021.0318.

Reproductive, Developmental and Aging Sciences

3. Aging Sciences

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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 five 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) Biomarkers of dementia, caregiver's stress and geriatric syndromes
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 metabolic diseases and pulmonary aging

Publications (Original Articles)

1. 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 Jul-Aug;101:104661. doi: 10.1016/j.archger.2022.104661.
2. Azuma K, Ikeda K, Suzuki T, Aogi K, Horie-Inoue K, Inoue S. TRIM47 activates NF-κB signaling via PKC-ε/PKD3 stabilization and contributes to endocrine therapy resistance in breast cancer. *Proc Natl Acad Sci U S A*. 2021

Aug 31;118(35): e2100784118. doi: 10.1073/pnas.2100784118.

3. Azuma K, Osuka Y, Kojima N, Sasai H, Kim H, Inoue S. Association of Vitamin K Insufficiency With Cognitive Dysfunction in Community-Dwelling Older Adults. *Front Nutr.* 2022 Jan 31; 8: 811831. doi:10.3389/fnut.2021.811831. eCollection 2021.
4. Cherbuin N, Iijima K, Kalula S, Malhotra R, Rasmussen L, Chan A, Lafortune L, Harper S, Zheng X, Lindeman D, Walsh E, Hussain R, Burns R, Kristiansen M, Sugawara I, Son BK, Tanaka T, Buckner S, Hoffman J, Combrinck M. SOCIETAL NEED FOR INTERDISCIPLINARY AGEING RESEARCH An International Association of Research Universities "Ageing, Longevity, and Health" Stream (IARU-ALH) position statement. *Biomed Hub.* 2021;6:42-47.
5. Fitriana I, Setiati S, Rizal EW, Istanti R, Rinaldi I, Kojima T, Akishita M, Azwar MK. Malnutrition and depression as predictors for 30-day unplanned readmission in older patient: a prospective cohort study to develop 7-point scoring system. *BMC Geriatr.* 2021;21(1):256.
6. Gong Q, Ishii M, Numata O, Xie W, Hirata T. Utility of a shortened Hasegawa Dementia Scale Revised questionnaire to rapidly screen and diagnose Alzheimer's disease. *Aging Med.* 2021 Jun 8;4(2):109-114. doi: 10.1002/agm2.12152. eCollection 2021.
7. Hamada S, Kojima T, Hattori Y, Maruoka H, Ishii S, Okochi J, Akishita M. Use of psychotropic drugs and drugs with anticholinergic properties among residents with dementia in intermediate care facilities for older adults in Japan: a cohort study. *BMJ Open.* 2021;11(4):e045787.
8. Handa N, Mitsutake S, Ishizaki T, Nakabayashi T, Akishita M, Tamiya N, Yoshie S, Iijima K. Associations of coprescribed medications for chronic comorbid conditions in very old adults with clinical dementia: a retrospective cohort study using insurance claims data. *BMJ Open.* 2021;11:e043768. doi: 10.1136/bmjopen-2020-043768. PMID: 34266835; PMCID: PMC8286766.
9. Iijima K, Arai H, Akishita M, Endo T, Ogasawara K, Kashihara N, Hayashi K. Y, Yumura W, Yokode M, Ouchi Y. Toward the development of a vibrant, super-aged society: The future of medicine and society in Japan, *Geriatr Gerontol Int.* 2021.5 doi: 10.1111/ggi.14201
10. Iki M, FujimoriK, 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.* 2022 Mar 26:116396. doi: 10. 1016/j.bone.2022.116396. Online ahead of print.
11. Iki M, FujimoriK, 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.* 2022 Jan 13. doi: 10.1007/s00198-021-06265-y. Online ahead of print.
12. 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.* 2022 Feb 19;22(1):145. doi: 10.1186/ s12877-022-02841-x.
13. Ito T, Mori T, Takahashi H, Shimafuji N, Iijima K, Yoshie S, Tamiya N. Prevention services via public long-term care insurance can be effective among a specific group of older adults in Japan. *BMC Health Services Research*. 2021.5 21:531 https://doi.org/10.1186/s12913-021-06495-0
14. 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.* 2022 Jan 27. doi: 10.2186/jpr.JPR_D_21_00272. Online ahead of print.
15. Jung HW, Lim WS, Cesari M, Auyeung TW, Kojima T, Ga H, Cameron ID, Lim JY. Challenges and Opportunities for Academic Journals to Serve the Older Population in Western Pacific Region. *Ann Geriatr Med Res.* 2021;25(4):231-236.

16. 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.* 2022 Jan;22(1): 26-31. doi: 10.1111/ggi.14307.
17. Kikuchi K, Tatebe T, Sudo Y, Yokoyama M, Kidana K, Chiu YW, Takatori S, Arita M, Hori Y, Tomita T. GPR120 signaling controls amyloid-β degrading activity of matrix metalloproteinases. *Journal of Neuroscience.* 2021;41(28):6173-6185.
18. Konno D, Ikegaya Y, Sasaki T. Weak representation of awake/sleep states by local field potentials in aged mice. *bioRxiv*. https://doi.org/ 10.1101/2021.10.13.464191, 2021.
19. Konno D, Nishimoto S, Suzuki T, Ikegaya Y, Matsumoto N. Multiple states in ongoing neural activity in the rat visual cortex. *PLoS One*. 16(8): e0256791., 2021.
20. Kunieda K, Fujishima I, Wakabayashi H, Ohno T, Shigematsu T, Itoda M, Mori T, Machida N, Ogawa S. Relationship between tongue pressure and pharyngeal function using high resolution manometry in older dysphagia patients with sarcopenia. *Dysphargia.* 36:33-40,2021.
21. 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.* 2022 Mar 30. Online ahead of print.
22. Mori T, Wakabayashi H, Ogawa N, Fujishima I, Oshima F, Itoda M, Kunieda K, Shigematsu T, Nishioka S, Tohara H, Yamada M, Ogawa S. The mass of the geniohyoid muscle is associated with maximum tongue pressure and tongue area in patients with sarcopenic dysphagia. *J. Nutr Health Aging.* 25:356-360,2021.
23. Nakamura M, Okajima K, Matsumoto Y, Tanaka T, Iijima K, Nihei M. Effectiveness of Continuous Grip Strength Measurement using Social Assistive Robots on Older adults at Home. *Journal of Robotics and Mechatronics*. 33(4):719-729. doi: 10.20965/jrm.2021.p0719
24. Nakatoh S, Fujimori K, Ishii S, Tamaki J, Okimoto N, Ogawa S, Iki M. Insufficient increase in bone mineral density testing rates and pharmacotherapy after hip and vertebralfracture: Analysis from National Database of Health Insurance Claims in Japan. *Arch Osteoporos.* 16:130,2021.
25. Nakatoh S, Fujimori K, Ishii S, Tamaki J, Okimoto N, Ogawa S, Iki M. Insufficient persistence of and adherence to osteoporosis pharmacotherapy: Analysis from National Database of Health Insurance Claims in Japan. *Arch Osteoporos.* 16:131,2021.
26. Nakatoh S, Fujimori K, Tamaki J, Okimoto N, Ogawa S, Iki M. Insufficient persistence and adherence to osteoporosis pharmacotherapy in Japan. *J Bone Miner Metab.* 39:501-509,2021.
27. Ogawa N, Wakabayashi H, Mori T, Fujishima I, Oshima F, Itoda M, Kunieda K , Shigematsu T, Nishioka S, Tohara H, Ohno T, Nomoto A, Shimizu A, Yamada M, Ogawa S. Digastric muscle mass and intensity in older patients with sarcopenic dysphagia by ultrasonography. *Geriatr. Gerontol. Int.* 21:14-19,2021.
28. Ogura T, Azuma K, Sato J, Kinowaki K, Takayama KI, Takeiwa T, Kawabata H, Inoue S. OCT1 Is a Poor Prognostic Factor for Breast Cancer Patients and Promotes Cell Proliferation via Inducing NCAPH. *Int J Mol Sci.* 2021 Oct 25;22(21):11505. doi: 10.3390/ijms222111505.
29. Ogura T, Azuma K, Takeiwa T, Sato J, Kinowaki K, Ikeda K, Kawabata H, Inoue S. TRIM39 is a poor prognostic factor for patients with estrogen receptor-positive breast cancer and promotes cell cycle progression. *Pathol Int.* 2022 Feb;72(2):96-106. doi: 10.1111/pin.13190.
30. Okamoto S, Ishii M, Hibi S, Akishita M, Yamaguchi Y. Breathing irregularities before sleep onset on polysomnography in patients with heart diseases. *Sleep Breath.* 2022 Jun;26(2):605-612. doi: 10.1007/s11325-021-02403-2.
31. Sato J, Azuma K, Kinowaki K, Ikeda K, Ogura T, Takazawa Y, Kawabata H, Kitagawa M, Inoue S. Combined Use of Immunoreactivities of RIG-I with Efp/TRIM25 for Predicting Prognosis of Patients With Estrogen Receptor-positive Breast Cancer. *Clin Breast Cancer.* 2021 Oct;21(5):399-407.e2. doi: 10.1016/j.clbc.2020.12.001.

32. Sawada M, Kubota N, Sekine R, Yakabe M, Kojima K, Umeda-Kameyama Y, Akishita M, Ogawa S. Sex-related differences in the effects of nutritional status and body composition on functional disability in the elderly. *PLOS ONE.* 16:e0246276,2021.
33. Shibasaki K, Asahi T, Kuribayashi M, Tajima Y, Marubayashi M, Iwama R, Akishita M, Ogawa S. Potential prescribing omissions of anti-osteoporosis drugs is associated with rehabilitation outcomes after fragility fracture: Retrospective cohort study. *Geriatr Gerontol Int.* 2021 May; 21(5):386-391. doi: 10.1111/ggi.14145.
34. Shirobe M, Watanabe Y, Tanaka T, Hirano H, Kikutani T, Nakajo K, Sato T, Furuya J, Minakuchi S, Iijima K. Effect of an Oral Frailty Measures Program on Community-Dwelling Elderly People: A Cluster-Randomized Controlled Trial, *Gerontology*, 2022;68(4):377-386. doi: 10.1159/000516968.
35. Son BK, Akishita M, Yamanaka T, Toyoshima K, Tanaka T, Suthutvoravut U, Iijima K. Association between inflammatory potential of the diet and sarcopenia/its components in community-dwelling older Japanese men. *Arch Gerontol Geriatr.* 2021;97:104481. doi: 10.1016/j.archger.2021.104481.
36. 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.
37. Takamatsu K, Tanaka J, Katada R, Azuma K, Takakura I, Aota K, Kamatani T, Shirota T, Inoue S, Mishima K. Aging-associated stem/progenitor cell dysfunction in the salivary glands of mice. *Exp Cell Res.* 2021 Dec 1;409(1):112889. doi: 10.1016/j.yexcr.2021.112889.
38. Tamiya H, Yasunaga H, Hosoi T, Yamana H, Matsui H, Fushimi K, Akishita M, Ogawa S. Association between protein intake and mortality in older patients receiving parenteral nutrition: a retrospective observational study. *Am J Clin Nutr.* 2021 Sep 28:nqab292. doi: 10.1093/ajcn/nqab292.
39. Tanaka T, Hirano H, Ohara Y, Nishimoto M, Iijima K. Oral Frailty Index-8 in the risk assessment of new-onset oral frailty and functional disability among community-dwelling older adults. *Arch Geront Geriatr.* May-Jun 2021; 94: 104340. doi: 10.1016/j.archger.2021.104340.
40. 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* 2022 Mar 17: 1–5. doi: 10.14283/ jfa.2022.20.
41. Tanaka T, Son BK, Lyu W, Iijima K. Impact of social engagement on the development of sarcopenia among community-dwelling older adults: A Kashiwa cohort study. *Geriatr Gerontol Int*. First published: 23 March 2022 https://doi.org/10.1111/ggi.14372
42. 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.
43. 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 older adults. *Geriatr Gerontol Int*. 2022 Feb;22(2):127-131. doi: 10.1111/ggi.14328.
44. Yamada Y, Kojima T, Umeda-Kameyama Y, Ogawa S, Eto M, Akishita M. Outcomes of anticoagulant prescribing for older patients with atrial fibrillation depends on disability level provided by long-term care insurance. *Arch Gerontol Geriatr*. 2021;96:104434.
45. Yamamoto H, Sazuka M, Ishibashi M, Nogimori C, Takada K, Hamaya H, Yamada H, Awata. DASC-21: a novel geriatric assessment for discriminating best supportive care in older patients with inoperable advanced non-small cell lung cancer. *S.Jpn J Clin Oncol.* 2021 Nov 1;51(11):1628-1635.
46. 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;45:612-619. doi: 10.1038/s41440-022-00861-z.

47. Yamasaki T, Ikawa F, Hidaka T, Kuwabara M, Matsuda S, Ozono I, Chiku M, Kitamura N, Hamano T, Akishita M, Yamaguchi S, Tomimoto H, Suzuki M. Prevalence and risk factors for brain white matter changes in young and middle-aged participants with Brain Dock (brain screening): a registry database study and literature review. *Aging (Albany NY).* 2021;13:9496-9509. doi: 10.18632/aging.202933.
48. Yoshizawa Y, Tanaka T, Takahashi K, Mahiro Fujisaki-Sueda-Sakai M, Son BK, Iijima K. Impact of Health Literacy on the Progression of Frailty after Four Years among Community-dwelling Older Adults. *Int J Env Res Pub Health.* 2022;19(1): 394. doi: 10.3390/ijerph19010394.

Surgical Sciences

1. Surgery

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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). Nakajima, Jun has taken over the mission of the department since April 2011.

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.

Clinical activities

Five staffs (Nakajima J, Sato M, Konoeda C, Nagano M, and Nakao K), 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 para-neoplastic 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 113 lung transplants (including 24 living related donor lung trans-plantations) to date.

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 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 and trachea after allogeneic transplantation.
(8) Regeneration of the acellularized allogeneic lung with autologous cell seeding
(9) Research on extracorporeal membranous oxygenation for bridge use to lung transplantation

Selected publications (2021)

1. Konoeda C, Sato M, Nagayama K, Nakajima J. Simultaneous single lobar lung transplantation and contralateral lung volume reduction. Eur J Cardiothorac Surg. 2021; 59(6):1342-1344
2. Shiono S, Matsutani N, Hashimoto H, Yamauchi Y, Matsuguma H, Mun M, Kuroda H, Funai K, Nakajima J, Kawamura M; Metastatic Lung Tumor Study Group of Japan. Prospective study of recurrence at the surgical margin after wedge resection of pulmonary metastases. Gen Thorac Cardiovasc Surg. 2021; 69(6):950-959
3. Hirata T, Koga K, Taniguchi F, Takazawa N, Honda R, Tanaka T, Kurihara M, Nakajima J, Yoshimura K, Kitade M, Narahara H, Kitawaki J, Harada T, Katabuchi H, Horie S, Osuga Y. National survey of bladder endometriosis cases in Japan. J Obstet Gynaecol Res. 2021; 47(4):1451-1461
4. 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 2021; 35(1):239-248
5. Yoshiyasu N, Sato M, Konoeda C, Nakajima J. Management of partial anomalous pulmonary venous return in lung transplantation. Ann Thorac Surg. 2021; 112(2):e95-e97
6. Iida T, Sato M, Nakajima J. Resection of clustered arteriovenous malformations to avoid lung transplantation. Ann Thorac Surg. 2021; 112(4):e253-e256
7. Shiiya H, Nakajima J, Date H, Chen-Yoshikawa TF, Tanizawa K, Handa T, Oto T, Otani S, Shiotani T, Okada Y, Matsuda Y, Shiraishi T, Moroga T, Minami M, Funaki S, Chida M, Yoshino I, Hatachi G, Uemura Y, Sato M. Outcomes of lung transplantation for idiopathic pleuroparenchymal fibroelastosis. Surg Today. 2021; 51(8):1276-1284.
8. Yoshiyasu N, Sato M, Urushiyama H, Aoyama A, Date H, Nakajima J. Familial interstitial pneumonia revealed after living-donor lobar lung transplantation. Ann Thorac Surg. 2021; 112(5): e365-e368
9. Nobori Y, Sato M, Morota M, Shinohara Y, Yoshida D, Karasaki T, Kitano K, Nakajima J. Lung autotransplantation for bronchial necrosis after radiotherapy: a case report. Surg Case Rep. 2021; 7(1):79
10. Yoshiyasu N, Sato M, Konoeda C, Nakajima J. Pediatric living-donor lobar lung transplantation in postpneumonectomy-like anatomy caused by pulmonary hypoplasia with congenital diaphragmatic hernia. Am J Transplant. 2021; 21(10):3461-3464
11. Nobori Y, Sato M, Hirata Y, Yamauchi H, Konoeda C, Kitano K, Nakajima J. Intrabronchial migration of hemostatic agent through a bronchial fistula after lung transplantation: a case report. Surg Case Rep. 2021; 7(1):116.
12. Yoshiyasu N, Sato M, Nakajima D, Tomioka Y, Watanabe Y, Shiraishi T, Funaki S, Maeda S, Tomoshige K, Nakajima T, Tsuchiya T, Sugimoto S, Yoshino I, Nagayasu T, Chida M, Minami M, Okada Y, Toyooka S, Date H, Nakajima J. Current status of inhaled nitric oxide therapy for lung transplantation in Japan: a nationwide

survey. Gen Thorac Cardiovasc Surg. 2021; 69(10):1421-1431
13. Nagayama K, Kitano K, Yoshiyasu N, Nakajima J. Lobectomy for lung cancer in a patient with Fontan circulation: A case report. JTCVS Tech. 2021; 6:163-165
14. Yoshiyasu N, Sato M, Anraku M, Ichiba S, Nakajima J. Lung transplant after long-term veno-venous extracorporeal membrane oxygenation: a case report. J Cardiothorac Surg. 2021; 16(1):246.
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; 35(6):3125-3135
16. Sun C, Nagaoka K, Kobayashi Y, Nakagawa H, Kakimi K, Nakajima J. Neoantigen Dendritic Cell Vaccination Combined with Anti-CD38 and CpG Elicits Anti-Tumor Immunity against the Immune Checkpoint Therapy-Resistant Murine Lung Cancer Cell Line LLC1. Cancers (Basel). 2021; 13(21):5508
17. Sun C, Anraku M, Nakajima J. ASO Author Reflections: An Evolving Skeletal Muscle Profiling-Towards Precise Host Phenotype and Prognostic Stratification in Non-small Cell Lung Cancer. Ann Surg Oncol. 2022; 29(3):1825-182
18. Maeda Y, Wada H, Sugiyama D, Saito T, Irie T, Itahashi K, Minoura K, Suzuki S, Kojima T, Kakimi K, Nakajima J, Funakoshi T, Iida S, Oka M, Shimamura T, Doi T, Doki Y, Nakayama E, Ueda R, Nishikawa H. Depletion of central memory CD8+ T cells might impede the antitumor therapeutic effect of Mogamulizumab. Nat Commun. 2021; 12(1):7280
19. Saito T, Kurose K, Kojima T, Funakoshi T, Sato E, Nishikawa H, Nakajima J, Seto Y, Kakimi K, Iida S, Doki Y, Oka M, Ueda R, Wada H. Phase Ib study on the humanized anti-CCR4 antibody, KW-0761, in advanced solid tumors. Nagoya J Med Sci. 2021; 83(4):827-840
20. Nagano M, Kohsaka S, Hayashi T, Ueno T, Kojima S, Shinozaki-Ushiku A, Morita S, Tsuda M, Tanaka S, Shinohara T, Omori Y, Sugaya F, Kato H, Narita Y, Nakajima J, Suzuki K, Takamochi K, Mano H. Comprehensive molecular profiling of pulmonary pleomorphic carcinoma. NPJ Precis Oncol. 2021
21. Tian D, Shiiya H, Sato M, Nakajima J. Tumor Maximum Area May Determine the Survival Outcomes of Patients with Thymic Epithelial Tumors. Ann Surg Oncol. 2021;28(4):2078-2085
22. Tian D, Yan HJ, Nakajima J. ASO Author Reflections: Tumor Maximum Area is Better for Representing Tumor Size in Thymic Epithelial Tumors. Ann Surg Oncol. 2021; 28(4):2086-2087
23. Tian D, Nakajima J. Reply to "Euclidean Geometry Versus Metabolic Biochemistry in the Prognostic Evaluation of the Thymic Epithelial Tumours". Ann Surg Oncol. 2021; 28(7):4060-4061
24. Konoeda C, Sato M, Hirata Y, Nakajima J. Native Lung Pulmonary Artery Banding After Single-Lung Transplant for Obliterative Bronchiolitis. Ann Thorac Surg. 2021;111(4):e253-e255.
25. Yanagiya M, Kitano K, Yotsumoto T, Asahina H, Nagayama K, Nakajima J. Transplantation of Bioengineered Lungs Created From Recipient-Derived Cells Into a Large Animal Model. Semin Thorac Cardiovasc Surg. 2021; 33(1):263-271

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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 380, 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 2022, 176 cases of heart transplantation including 15 pediatric patients and 382 cases of ventricular assist device (VAD) implantation including 262 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 cardio-vascular 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. Bujo C, Amiya E, Hatano M, Tsuji M, Maki H, Ishida J, Ishii S, Narita K, Endo M, Ando M, Shimada S, Kinoshita O, Ono M, Komuro I. Association between infectious event and de novo malignancy after heart transplantation. Heart Vessels. 2021 Apr;36 (4): 499-508. PMID: 33140148.
2. Kohno H, Matsumiya G, Sawa Y, Fukushima N, Saiki Y, Shiose A, Ono M. Can the intermittent low-speed function of left ventricular assist device prevent aortic insufficiency? J Artif Organs. 2021 Jun; 24(2): 191-198. PMID: 33420874.
3. Tsuji M, Amiya E, Bujo C, Hara T, Saito A, Minatsuki S, Maki H, Ishida J, Hosoya Y, Hatano M, Imai H, Nemoto M, Kagami Y, Endo M, Kimura M, Ando M, Shimada S, Kinoshita O, Ono M, Komuro I. Carbon Monoxide Diffusing Capacity Predicts Cardiac Readmission in Patients Undergoing Left Ventricular Assist Device Implantation in Japan. ASAIO J. 2021 Oct 1;67(10):1111-1118. PMID: 33470633.
4. Goto H, Komae H, Sekine H, Homma J, Lee S, Yokota T, Matsuura K, Someya T, Ono M, Shimizu T. Continuous measurement of surface electrical potentials from transplanted cardio-myocyte tissue derived from human-induced pluripotent stem cells under physiological conditions in vivo. Heart Vessels. 2021 Jun;36(6):899-909. PMID: 33683408.
5. 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. PMID: 34697143
6. Chang D, Fan T, Gao S, Jin Y, Zhang M, Ono M. Application of mesenchymal stem cell sheet to treatment of ischemic heart disease. Stem Cell Res Ther. 2021 Jul 7;12(1):384. PMID: 34233729
7. Shimamura J, Nishinaka T, Mizuno T, Tsukiya T, Inatomi A, Kobayashi F, Katagiri N, Takewa Y, Nishimura T, Ono M, Tatsumi E. Assessment of ocular blood flow in continuous-flow ventricular assist device by laser speckle flowgraphy. J Artif Organs. 2021 Dec;24(4):419-424. PMID: 33825101.
8. Takeda N, Inuzuka R, Yagi H, Morita H, Ando M, Yamauchi H, Taniguchi Y, Porto KJ, Kanaya T, Ishiura H, Mitsui J, Tsuji S, Toda T, Ono M, Komuro I. Clinical Impact of Copy Number Variation on the Genetic Diagnosis of Syndromic Aortopathies. Circ Genom Precis Med. 2021 Aug; 14(4): e003458. PMID: 34325513.
9. Yakuwa K, Miyaji K, Kitamura T, Miyamoto T, Ono M, Kaneko Y. Neutrophil-to-lymphocyte ratio is prognostic factor of prolonged pleural effusion after pediatric cardiac surgery. JRSM Cardiovasc Dis. 2021 Apr 19;10:2048004021100 9438. doi: 10.1177/20480040211009438. PMID: 34262699
10. Kinugawa K, Sakata Y, Ono M, Nunoda S, Toda K, Fukushima N, Shiose A, Oishi S, Yumino D, Imamura T, Endo M, Hori Y, Kashiwa K, Aita K, Kojin H, Tejima Y, Sawa Y. Consensus Report on Destination Therapy in Japan - From the DT Committee of the Council for Clinical Use of Ventricular Assist Device Related Academic Societies. Circ J. 2021 Sep 24;85(10): 1906-1917. PMID: 34433758.
11. Bujo C, Amiya E, Hatano M, Ishida J, Tsuji M, Kakuda N, Narita K, Saito A, Yagi H, Ando M, Shimada S, Kimura M, Kinoshita O, Ono M, Komuro I. Long-Term renal function after implantation of continuous-flow left ventricular assist devices: A single center study. Int J Cardiol Heart Vasc. 2021 Nov 1;37, PMID: 34765720
12. 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 Jan; 52(1): 22-35. PMID: 34783905.

13. Aoyama G, Zhao L, Zhao S, Xue X, Zhong Y, Yamauchi H, Tsukihara H, Maeda E, Ino K, Tomii N, Takagi S, Sakuma I, Ono M, Sakaguchi T. Automatic Aortic Valve Cusps Segmentation from CT Images Based on the Cascading Multiple Deep Neural Networks. J Imaging. 2022 Jan 14;8(1):11. doi: 10.3390/jimaging8010011. PMID: 35049852.
14. Terakawa K, Yamauchi H, Lee Y, Ono M. A Novel Knitted Polytetrafluoroethylene Patch for Cardiovascular Surgery. Int Heart J. 2022;63(1): 122-130. PMID: 35095061.
15. Ando M, Yamauchi H, Gyoten T, Komae H, Hoshino Y, Itoda Y, Shimada S, Kimura M, Kinoshita O, Ono M. Association between left ventricular ejection fraction and mortality after Bentall procedure. Heart Vessels. 2022 Feb 5. doi: 10.1007/s00380-022-02028-9. Epub ahead of print. PMID: 35124729.
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. PMID: 35146960.
17. Myers PO, Dayan V, Szeto WY, Thourani VH, Malaisrie SC, Moon MR, Prager RL, Ono M, Okita Y, Freemantle N, Milojevic M. Joint surgical associations (EACTS, LACES, ASCVTS, AATS, and STS) position statement regarding the VARC-3 definitions for aortic valve clinical research. J Thorac Cardiovasc Surg. 2022 May; 163(5): 1792-1794. PMID: 35307218.
18. Kida K, Kanaki T, Gao S, Hatanaka D, Iwakami M, Liu S, Horikawa M, Ono M, Chang D. A Novel 3D Culture System Using a Chitin-Based Polysaccharide Material Produces High-Quality Allogeneic Human UCMSCs with Dispersed Sphere Morphology. Cells. 2022 Mar 15;11(6): 995. PMID: 35326446.
19. Ono M. Updating guidelines: When is the best timing of upgrading recommendation for an emerging technology? Asian Cardiovasc Thorac Ann. 2021 May;29(4):250-253. PMID: 34053247.
20. Kitaoka H, Tsutsui H, Kubo T, Ide T, Chikamori T, Fukuda K, Fujino N, Higo T, Isobe M, Kamiya C, Kato S, Kihara Y, Kinugawa K, Kinugawa S, Kogaki S, Komuro I, Hagiwara N, Ono M, Maekawa Y, Makita S, Matsui Y, Matsushima S, Sakata Y, Sawa Y, Shimizu W, Teraoka K, Tsuchihashi-Makaya M, Ishibashi-Ueda H, Watanabe M, Yoshimura M, Fukusima A, Hida S, Hikoso S, Imamura T, Ishida H, Kawai M, Kitagawa T, Kohno T, Kurisu S, Nagata Y, Nakamura M, Morita H, Takano H, Shiga T, Takei Y, Yuasa S, Yamamoto T, Watanabe T, Akasaka T, Doi Y, Kimura T, Kitakaze M, Kosuge M, Takayama M, Tomoike H; Japanese Circulation Society Joint Working Group. JCS/JHFS 2018 Guideline on the Diagnosis and Treatment of Cardiomyopathies. Circ J. 2021 Jul 22. doi: 10.1253/circj.CJ-20-0910. Epub ahead of print. PMID: 34305070.
21. Chang D, Fan T, Gao S, Jin Y, Zhang M, Ono M. Application of mesenchymal stem cell sheet to treatment of ischemic heart disease. Stem Cell Res Ther. 2021 Jul 7;12(1):384. PMID: 34233729.
22. Tsutsui H, Ide T, Ito H, Kihara Y, Kinugawa K, Kinugawa S, Makaya M, Murohara T, Node K, Saito Y, Sakata Y, Shimizu W, Yamamoto K, Bando Y, Iwasaki YK, Kinugasa Y, Mizote I, Nakagawa H, Oishi S, Okada A, Tanaka A, Akasaka T, Ono M, Kimura T, Kosaka S, Kosuge M, Momomura SI. JCS/JHFS 2021 Guideline Focused Update on Diagnosis and Treatment of Acute and Chronic Heart Failure. J Card Fail. 2021 Dec;27(12):1404-1444. PMID: 34600838.
23. Ono M. Durable Ventricular Assist Device for Bridge to Transplantation. In: Fukushima N, editor. Heart Transplantation. London: Intech Open; 2022 [cited 2022 Feb 05]. Available from: https://www.intechopen.com/online-first/80317 doi: 10.5772/intechopen.102467
24. Nakamura M, Yaku H, Ako J, Arai H, Asai T, Chikamori T, Daida H, Doi K, Fukui T, Ito T, Kadota K, Kobayashi J, Komiya T, Kozuma K, Nakagawa Y, Nakao K, Niinami H, Ohno T, Ozaki Y, Sata M, Takanashi S, Takemura H, Ueno T, Yasuda S, Yokoyama H, Fujita T, Kasai T, Kohsaka S, Kubo T, Manabe S, Matsumoto N,

Miyagawa S, Mizuno T, Motomura N, Numata S, Nakajima H, Oda H, Otake H, Otsuka F, Sasaki KI, Shimada K, Shimokawa T, Shinke T, Suzuki T, Takahashi M, Tanaka N, Tsuneyoshi H, Tojo T, Une D, Wakasa S, Yamaguchi K, Akasaka T, Hirayama A, Kimura K, Kimura T, Matsui Y, Miyazaki S, Okamura Y, Ono M, Shiomi H, Tanemoto K; Japanese Circulation Society Joint Working Group. JCS/JSCVS 2018 Guideline on Revascularization of Stable Coronary Artery Disease. Circ J. 2022 Feb 25;86(3):477-588. PMID: 35095031.

25. Koizumi J, Iwase T, Tsuji S, Goto T, Oyama K, Kin H. Intrapulmonary artery septation for unilateral absence of the pulmonary artery. Asian Cardiovasc Thorac Ann. 2022 May;30(4):477-479. PMID: 33926269.
26. Tsuji S, Ikai A, Oyama K, Kin H, Koizumi J. Outcomes of primary sternal closure for postoperative mediastinitis in children. Eur J Cardiothorac Surg. 2021 May 8;59(5):951-957. PMID: 33576375.
27. Hirata Y, Hirahara N, Murakami A, Motomura N, Miyata H, Takamoto S. Status of cardiovascular surgery in Japan: A report based on the Japan Cardiovascular Surgery Database 2017-2018. 1. Congenital heart surgery. Asian Cardiovasc Thorac Ann. 2021 May;29(4):289-293. PMID: 33375819.
28. Ide Y, Tachimori H, Hirata Y, Hirahara N, Ota N, Sakamoto K, Ikeda T, Minatoya K. Risk analysis for patients with a functionally univentricular heart after systemic-to-pulmonary shunt placement. Eur J Cardiothorac Surg. 2021 Jul 30; 60(2):377-383. PMID: 33712829.
29. Hörer J, Hirata Y, Tachimori H, Ono M, Vida V, Herbst C, Kansy A, Jacobs JP, Tobota Z, Sakamoto K, Ebels T, Maruszewski B. Pediatric Cardiac Surgical Patterns of Practice and Outcomes in Japan and Europe. World J Pediatr Congenit Heart Surg. 2021 May;12(3):312-319. PMID: 33942682.
30. Ota N, Tachimori H, Hirata Y, Miyata H, Suzuki T, Uchita S, Takamoto S, Izutani H. Contemporary patterns of the management of truncus arteriosus (primary versus staged repair): outcomes from the Japanese National Cardiovascular Database. Eur J Cardiothorac Surg. 2022 Mar 24;61(4):787-794. PMID: 34329388.
31. Matsui H, Hirata Y, Inuzuka R, Hayashi T, Nagamine H, Ueda T, Nakayama T. Initial national investigation of the prenatal diagnosis of congenital heart malformations in Japan-Regional Detection Rate and Emergency Transfer from 2013 to 2017. J Cardiol. 2021 Dec;78(6):480-486. PMID: 34454809.
32. 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. 2021 Dec 16: jmedgenet-2021-108186. PMID: 34916231.

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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. Under the supports by the Social Medical Corporation Sosaikoseikai, the Social Medical Corporation Kawakita Medical Foundation and RIZAP Group Inc., Bariatric & Metabolic care (social cooperation program) was newly established 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, 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 or three 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, trans-mediastinal (non-transthoracic) radical esophag-ectomy 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, Thursday, and Friday morning, respectively, and a journal club on Monday. We also have a specialized upper gastrointestinal case conference on Wednesday evening. Further, cancer board is held bi-weekly, where the radiologists and endoscopists 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 70 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. Mori K, Sugawara K, Aikou S, Yamashita H, Yamashita K, Ogura M, et al. Esophageal cancer patients' survival after complete response to definitive chemoradiotherapy: a retrospective analysis. Esophagus 2021 Jul;18(3):629-637.

2. Ogane K, Uenomachi M, Shimazoe K, Takahashi M, Takahashi H, Seto Y, et al. Simultaneous measurements of single gamma ray of (131)I and annihilation radiation of (18)F with Compton PET hybrid camera. Appl Radiat Isot 2021 Oct; 176:109864.
3. Sato Y, Mori K, Hirano K, Yagi K, Kobayashi Y, Nagaoka K, et al. Adoptive γδT-cell transfer alone or combined with chemotherapy for the treatment of advanced esophageal cancer. Cytotherapy 2021 May;23(5):423-432.
4. Seto Y. Sarcopenia, muscle quality, and gastric cancer surgery. Ann Gastroenterol Surg 2021 Jul 12;5(4):402-403.
5. Seto Y, Mori K, Yamagata Y, Aikou S, Yagi K, Nishida M, et al. □. Robot-Assisted Trans-mediastinal Esophagectomy for Esophageal Cancer. Gan To Kagaku Ryoho 2021 Sep;48(9): 1110-1114
6. Shiomi S, Toriumi T, Yagi K, Asaoka R, Okumura Y, Wakamatsu K, et al. Trunk fat volume can be a predictor of postoperative complications after gastrectomy: a retrospective cohort study. BMC Surg 2021 Apr 23;21(1):207-021-01221-3.
7. Sugawara K, Iwai M, Ito H, Tanaka M, Seto Y, Todo T. Oncolytic herpes virus G47Δ works synergistically with CTLA-4 inhibition via dynamic intratumoral immune modulation. Mol Ther Oncolytics 2021 May 19;22:129-142.
8. Sugawara K, Kawaguchi Y, Seto Y, Vauthey JN. Multidisciplinary treatment strategy for locally advanced gastric cancer: A systematic review. Surg Oncol 2021 Sep;38:101599.
9. Sugawara K, Yamashita H, Urabe M, Okumura Y, Yagi K, Aikou S, et al. Geriatric Nutrition Index Influences Survival Outcomes in Gastric Carcinoma Patients Undergoing Radical Surgery. JPEN J Parenter Enteral Nutr 2021 Jul;45(5): 1042-1051.
10. Sugawara K, Yamashita H, Urabe M, Okumura Y, Yagi K, Aikou S, et al. The different survival impacts of body mass index in elderly and non-elderly patients with gastric carcinoma. Surg Oncol 2021 Jun;37:101549.
11. Sugawara K, Yamashita H, Yajima S, Oshima Y, Mitsumori N, Fujisaki M, et al. Prognosis of hemodialysis patients undergoing surgery for gastric cancer: Results of a multicenter retro-spective study. Surgery 2021 Jul;170(1):249-256.
12. Yagi K, Toriumi T, Aikou S, Yamashita H, Seto Y. Salvage treatment after definitive chemoradiotherapy for esophageal squamous cell carcinoma. Ann Gastroenterol Surg 2021 Mar 10; 5(4):436-445.
13. Yajima S, Sugawara K, Iwai M, Tanaka M, Seto Y, Todo T. Efficacy and safety of a third-generation oncolytic herpes virus G47Δ in models of human esophageal carcinoma. Mol Ther Oncolytics 2021 Oct 30;23:402-411.
14. Yamashita S, Abe H, Kunita A, Yamashita H, Seto Y, Ushiku T. Programmed cell death protein 1/programmed death ligand 1 but not HER2 is a potential therapeutic target in gastric neuro-endocrine carcinoma. Histopathology 2021 Feb; 78(3):381-391.
15. Yasukawa Y, Hattori N, Iida N, Takeshima H, Maeda M, Kiyono T, et al. SAA1 is upregulated in gastric cancer-associated fibroblasts possibly by its enhancer activation. Carcinogenesis 2021 Feb 25;42(2):180-189.
16. Yoshimura S, Mori K, Ri M, Aikou S, Yagi K, Yamagata Y, et al. Comparison of short-term outcomes between transthoracic and robot-assisted transmediastinal radical surgery for esophageal cancer: a prospective study. BMC Cancer 2021 Mar 31;21(1):338-021-08075-1.

Hepato-biliary-Pancreatic Surgery Division and Artificial Organ and Transplantation Division

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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 125 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 (2021-2022)

1. Kiritani S, Kaneko J, Arita J, Ishizawa T, Akamatsu N, Hasegawa K. Radical antegrade modular pancreatosplenectomy for left-sided pancreatic ductal adenocarcinoma may reduce the local recurrence rate. Dig Surg. 2022 May 9. Online ahead of print.
2. Bae SK, Arita J, Akamatsu N, Maki H, Nishioka Y, Kawahara T, Miyata A, Kokudo T, Nagata R, Mihara Y, Ichida A, Inagaki Y, Kawaguchi Y, Ishizawa T, Kaneko J, Tamura S, Tanaka Y, Moriya K, Hasegawa K. The impact of the covalently closed circular DNA level on recurrence of hepatocellular carcinoma after initial hepatectomy: an analysis of patients with resolved hepatitis B virus infection. HPB (Oxford). 2022 Jul 1. Online ahead of print. PMID: 35863998
3. Matsumura M, Hasegawa K, Oba M, Yamaguchi K, Uetake H, Yoshino T, Morita S, Takahashi K, Unno M, Shimada Y, Muro K, Matsuhashi N, Mori M, Baba H, Shimada M, Mise Y, Kawaguchi Y, Kagimura T, Ishigure K, Saiura A, Sugihara K, Kokudo N. A randomized controlled trial of surgery and postoperative modified FOLFOX6 versus surgery and perioperative modified FOLFOX6 plus cetuximab in patients with KRAS wild-type resectable colorectal liver metastases: EXPERT study. Langenbecks Arch Surg. 2022 Feb 25.. Online ahead of print. PMID: 35211831
4. Watanabe G, Mise Y, Oba M, Saiura A, Inoue Y, Takahashi Y, Kishi Y, Suyama K, Takayama T, Noie T, Nishioka Y, Akamatsu N, Arita J, Kokudo N, Hasegawa K. A multicenter phase II trial evaluating the efficacy of bevacizumab plus mFOLFOX6 for R0 surgical resection in advanced colorectal liver metastases harboring mutant-type KRAS: NEXTO-mt trial. "HPB (Oxford). 2022 Aug;24(8):1245-1251.
5. Takahashi R, Akamatsu N, Nakazawa A, Nagata R, Ichida A, Kawaguchi Y, Ishizawa T, Kaneko J, Arita J, Hasegawa K. Effect of the response to preoperative treatment for hepatorenal syndrome on the outcome of recipients of living-donor liver transplantation. J Hepatobiliary Pancreat Sci. 2022 Jul;29(7):798-809.
6. Arita J, Ichida A, Nagata R, Mihara Y, Kawaguchi Y, Ishizawa T, Akamatsu N, Kaneko J, Hasegawa K. Conversion surgery after preoperative therapy for advanced hepatocellular carcinoma in the era of molecular targeted therapy and immune checkpoint inhibitors. J Hepatobiliary Pancreat Sci. 2022 Jul;29(7):732-740.
7. Komoto I, Kokudo N, Aoki T, Morizane C, Ito T, Hashimoto T, Kimura W, Inoue N, Hasegawa K, Kondo S, Ueno H, Igarashi H, Oono T, Makuuchi M, Takamoto T, Hirai I, Takeshita A, Imamura M. Phase I/II study of streptozocin monotherapy in Japanese patients with unresectable or metastatic gastroenteropancreatic neuroendocrine tumors. Jpn J Clin Oncol. 2022 Jul 8;52(7):708-716.
8. Maki H, Hasegawa K. Advances in the surgical treatment of liver cancer. "Biosci Trends. 2022 Jul 20;16(3):178-188.
9. Kazami Y, Kaneko J, Keshwani D, Takahashi R, Kawaguchi Y, Ichida A, Ishizawa T, Akamatsu N, Arita J, Hasegawa K. Artificial intelligence enhances the accuracy of portal and hepatic vein extraction in computed tomography for virtual hepatectomy. J Hepatobiliary Pancreat Sci. 2022 Mar;29(3):359-368.
10. Mochida S, Nakayama N, Terai S, Yoshiji H, Shimizu M, Ido A, Inoue K, Genda T, Takikawa Y, Takami T, Kato N, Abe M, Abe R, Inui A,

Ohira H, Kasahara M, Chayama K, Hasegawa K, Tanaka A. Diagnostic criteria for acute-on-chronic liver failure and related disease conditions in Japan. Hepatol Res. 2022 May; 52(5):417-421.

11. Abe H, Yasunaga Y, Yamazawa S, Nakai Y, Gonoi W, Nishioka Y, Murono K, Sasaki K, Arita J, Kawai K, Nozawa H, Hasegawa K, Ishihara S, Ushiku T. Histological growth patterns of colorectal cancer liver metastases: a strong prognostic marker associated with invasive patterns of the primary tumor and p53 alteration. Hum Pathol. 2022 May;123:74-83.
12. Watanabe G, Kawaguchi Y, Ichida A, Ishizawa T, Akamatsu N, Kaneko J, Arita J, Hasegawa K. Understanding conditional cumulative incidence of complications following liver resection to optimize hospital stay. HPB (Oxford). 2022 Feb; 24(2):226-233.
13. Ichida A, Akamatsu N, Nagata R, Mihara Y, Kawaguchi Y, Bae SK, Ishizawa T, Kaneko J, Arita J, Hasegawa K. Efficacy and Safety of Lenvatinib for the Treatment of Recurrent Hepatocellular Carcinoma After Living Donor Liver Transplantation: A Report of Two Cases. Anticancer Res. 2022 Feb;42(2):1161-1167.
14. Okada Y, Kawaguchi Y, Matsumura M, Matsubara S, Nakai Y, Ichida A, Ishizawa T, Akamatsu N, Kaneko J, Arita J, Koike K, Hasegawa K. A safe sequential treatment approach for patients who have acute cholecystitis with severe inflammation: Transmural gallbladder drainage followed by laparoscopic cholecystectomy under the guidance of fluorescence imaging. Asian J Endosc Surg. 2022 Jan;15(1):230-234.
15. Komagome M, Maki A, Nagata R, Masuda W, Kogure R, Mitsui T, Ninomiya R, Akamatsu N, Hasegawa K, Beck Y. Refractory Acute Antibody Mediated Rejection in Liver Transplant After Desensitization of Preformed Donor Specific Antibody-Validity of Bortezomib and Everolimus: A Case Report. Transplant Proc. 2022 Jan-Feb;54(1):147-152.
16. Kawaguchi Y, Fuks D, Vauthey JN, Kokudo N, Gayet B, Hasegawa K. A novel simple three-level liver resection classification without compromising the performance to predict surgical and postoperative outcomes. Eur J Surg Oncol. 2022 Jan;48(1):305-306.
17. Omichi K, Hasegawa K, Kumamaru H, Miyata H, Konno H, Seto Y, Mori M, Kokudo N. Association between age and short-term outcomes of gastroenterological surgeries in older patients: an analysis using the National Clinical Database in Japan. Langenbecks Arch Surg. 2021 Dec;406(8):2827-2836.
18. Watanabe T, Nakai Y, Mizuno S, Hamada T, Kogure H, Hirano K, Akamatsu N, Hasegawa K, Isayama H, Koike K. Prognosis of Primary Sclerosing Cholangitis According to Age of Onset. J Hepatobiliary Pancreat Sci. 2021 Dec; 28(12):1115-1120.
19. Iwano T, Yoshimura K, Watanabe G, Saito R, Kiritani S, Kawaida H, Moriguchi T, Murata T, Ogata K, Ichikawa D, Arita J, Hasegawa K, Takeda S. High-performance Collective Biomarker from Liquid Biopsy for Diagnosis of Pancreatic Cancer Based on Mass Spectrometry and Machine Learning. J Cancer. 2021 Nov 4; 12(24):7477-7487.
20. Kokudo T, Hasegawa K. Evaluating the liver function of patients with hepatocellular carcinoma. Hepatol Res. 2021 Nov;51(11):1095-1096.
21. Yamaguchi T, Hasegawa K, Sauvain MO, Passoni S, Kazami Y, Kokudo T, Cristaudi A, Melloul E, Uldry E, Kobayashi K, Akamatsu N, Kaneko J, Arita J, Sakamoto Y, Demartines N, Kokudo N, Halkic N. An aberrant right hepatic artery arising from the gastroduodenal artery: a pitfall encountered during pancreaticoduodenectomy. Surg Today. 2021 Oct;51(10):1577-1582.
22. Yasudo H, Ando T, Maehara A, Ando T, Izawa K, Tanabe A, Kaitani A, Nomura S, Seki M, Yoshida K, Oda H, Okamoto Y, Wang H, Kamei A, Kojima M, Kimura M, Uchida K, Nakano N, Kaneko J, Ebihara N, Hasegawa K, Shimizu T, Takita J, Ogawa H, Okumura K, Ogawa S, Tamura N, Kitaura J. A Possible Association Between a Nucleotide-Binding Domain LRR-Containing Protein Family PYD-Containing Protein 1 Mutation and an Autoinflammatory Disease Involving Liver Cirrhosis. Hepatology. 2021 Oct;74(4):2296-2299.

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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). 1812 operations were performed in 2021. The numbers of main operations are adrenalectomy 10, nephrectomy 28, partial nephrectomy 55, nephroureterectomy 19, radical cystectomy 14, radical prostatectomy 121, transurethral resection of the bladder tumor (TUR-Bt) 260, transurethral resection of the prostate (TUR-P) 15, and robot-assisted surgeries 188 (radical prostatectomy 121, partial nephrectomy 49, radical cystectomy 14, pyeloplasty 4).

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 21,456 patient-days from January 2021 to December 2021.

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. Watanabe D, Akiyama Y, Niimi A, Nomiya A, Yamada Y, Sato Y, Nakamura M, Kawai T, Yamada D, Suzuki M, Igawa Y, Kume H, Homma Y. Clinical characterization of interstitial cystitis/ bladder pain syndrome in women based on the presence or absence of Hunner lesions and glomerulations. Low Urin Tract Symptoms, 13(1), 139-143 202.1.
2. Kamei J, Aizawa N, Nakagawa T, Kaneko S, Fujimura T, Homma Y, Kume H, Igawa Y. Lacking transient receptor potential melastatin 2 attenuates lipopolysacchar ide□induced bladder inflammation and its associated hypersensitivity in mice. Int J Urol, 28(1),107-114,2021.1.
3. Yoshida S, Matsushima H, Fujii Y. Classification of oligometastatic prostate cancer with additional consideration for hormone sensitivity. World J Urol, Online ahead of print,2021.1.
4. Takemura K, Kawai T, Sato Y, Miyakawa J, Satoru Taguchi S, Akiyama Y, Yamada Y, Nakamura M, Yamada D, Suzuki M, Nakagawa T, Kume H. Impact of Initial Computed Tomography Findings on Management of Atypical Urinary Cytology of the Upper Urinary Tract. Urol Int,105(7-8), 619-623,2021.1.
5. Takeshima Y, Suzuki M, Miyakawa J, Tsuru I, Yamada Y, Nakamura M, Sato Y, Kawai T, Yamada D, Morikawa T, Kume H. Latent prostate cancer among Japanese males: a bibliometric study of autopsy reports from 1980-2016. Jpn J Clin Oncol, 51(1),156-159,2021.1.
6. Takeuchi T, Maki K, Okuno Y, Hattori-Kato M, Mikami K. Selection of AVP-shortage patients as candidates for low-dose oral desmopressin administration. Res Rep Urol,13,25-30,2021.1.
7. Taguchi S, Nakagawa T, Uemura Y, Akamatsu N, Gonoi W, Naito A, Kawai T, Kume H, Fukuhara H. Comparison of major definitions of sarcopenia based on the skeletal muscle index in patients with urothelial carcinoma. Future Oncology, 17, 197-203, 2021.1.
8. Inoue T, Okada S, Hamamoto S, Miura H, Matsuzaki J, Tambo M, Fukuhara H, Fujisawa M, Matsuda T, Nutahara K. Evaluation of flexible ureteroscope with an omni-directional bending

tip, using a JOYSTICK unit (URF-Y0016); an ex-vivo study. World Journal of Urology, 39, 209-215, 2021.1.

9. Akiyama Y, Zaitsu M, Watanabe D, Yoshimura I, Niimi A, Nomiya A, Yamada Y, Sato Y, Nakamura M, Kawai T, Yamada D, Suzuki M, Kume H, Homma Y. Relationship between the frequency of electrocautery of Hunner lesions and changes in bladder capacity in patients with Hunner type interstitial cystitis. Scientific Reports, 11(1), 105, 2021.1.
10. Akiyama Y, Yao JR, Kreder KJ, O'Donnell MA, Lutgendorf SK, Lyu D, Maeda D, Kume H, Homma Y, and Luo Y. Autoimmunity to urothelial antigen causes bladder inflammation, pelvic pain and voiding dysfunction: a novel animal model for Hunner type interstitial cystitis. American Journal of Physiology-Renal Physiology, 320(2), 174-182, 2021.2.
11. Shimizu T, Sugihara T, Kamei J, Takeshima S, Kinoshita Y, Kubo T, Shinzato T, Fujimura T, Yagisawa T. Predictive factors and management of urinary tract infections after kidney transplantation: a retrospective cohort study. Clin exp nephrol, 25(2), 200-206, 2021.2.
12. Matsumura S, Nakamori M, Tsuji T, Kato T, Nakamura M, Ojima T, Fukuhara H, Ino Y, Todo T, Yamaue H. Oncolytic virotherapy with SOCS3 enhances viral replicative potency and oncolysis for gastric cancer. Oncotarget, 12(4), 344-354, 2021.2.
13. Negishi T, Furubayashi N, Nakagawa T, Nishiyama N, Kitamura H, Hori Y, Kuroiwa K, Son Y, Seki N, Tomoda T, Okajima E, Nakamura M. Site-specific response to nivolumab in renal cell carcinoma. Anticancer Res, 41(3), 1539-1545, 2021.3.
14. Suzuki M, Kodaira M, Suyama K, MurataT, Kume H. Continence Status and Presence of Pressure Skin Injury Among Special Elderly Nursing Home Residents in Japan: A Nationwide Cross-Sectional Survey. Geriatrics(Basel), 6(2), 34, 2021.3.
15. Tsuru I, Niimi F, Honda S, Azuma T. Safety of same□day administration of gemcitabine plus cisplatin chemotherapy for urothelial carcinoma. Mol Clin Oncol, 14(3), 57, 2021.3.
16. Uemura H, Matsushima H, Kobayashi K, Mizusawa H, Nishimatsu H, Fizazi K, Smith M, Shore N, Tammela T, Tabata K I, Matsubara N, Iinuma M, Uemura H, Oya M, Momma T, Kawakita M, Fukasawa S, Kobayashi T, Kuss I, Le Berre M. A, Snapir A, Sarapohja T, Suzuki K. Efficacy and safety of darolutamide in Japanese patients with nonmetastatic castration-resistant prostate cancer: a sub-group analysis of the phase III ARAMIS trial. Int J Clin Oncol, 26(3), 578-590, 2021.3.
17. Taguchi S, Tambo M, Watanabe M, Machida H, Kariyasu T, Fukushima K, Shimizu Y, Okegawa T, Yokoyama K, Fukuhara H. Prospective Validation of Vesical Imaging-Reporting and Data System Using a Next-Generation Magnetic Resonance Imaging Scanner-Is Denoising Deep Learning Reconstruction Useful?. Int J Urol, 205(3), 205(3), 686-692, 2021.3.
18. Takeshima Y, Suzuki M, Ikegaya H, Idota N, Kawai T, Sato Y, Kume H. A cross-sectional cadaveric study of the correlation between genital organ measurements, serum testosterone, and serum prostate-specific antigen levels in Japanese male subjects. Int J Physiol Pathophysiol Pharmacol, 13(2), 36-42, 2021.4.
19. Kakutani S, Takeshima Y, Yamada Y, Fujimura T, Nagamoto S, Enomoto Y, Hakozaki Y, Kimura N, Teshima T, Akiyama Y, Sato Y, Kawai T, Yamada D, Kume H. Clinical significance and risk factors of urethrovesical anastomotic urinary leakage following robot-assisted radical prostatectomy: a multi-institutional study. BMC Urol, 21(1), 75, 2021.5.
20. Azuma T, Takeuchi T, Matayoshi Y, Namiki S, Obara T, Imamura K, Takamori M. Serum Alanine Aminotransferase as an Early Marker of Outcomes in Patients Receiving Anti-Pd-1 or Anti-Ctla-4 Antibody. Scientific Reports, 11(1), 10264, 2021.5.
21. Blas L, Onozawa M, Shiota M, Hinotsu S, Sakamoto S, Kitagawa Y, Kawai K, Eto M, Kume H, Akaza H, Japan Study Group of Prostate Cancer (J-CaP). Long-term outcomes of androgen deprivation therapy in prostate cancer among Japanese men over 80 years old. Cancer Sci, Online ahead of print, 2021.5.

22. Takahashi S, Takei M, Asakura H, Gotoh M, Ishizuka O, Kato K, Koyama M, Takeyama M, Tomoe H, Yamanishi T, Yokoyama O, Yoshida M, Yoshimura Y, Yoshizawa T. Clinical Guidelines for Female Lower Urinary Tract Symptoms (second edition). Int J Urol, 28(5), 474-492, 2021.5.
23. Takeshima Y, Yamada Y, Teshima T, Fujimura T, Kakutani S, Hakozaki Y, Kimura N, Akiyama Y, Sato Y, Kawai T, Yamada D, Kume H. Clinical significance and risk factors of International Society of Urological Pathology (ISUP) grade upgrading in prostate cancer patients undergoing robot-assisted radical prostatectomy. BMC Cancer, 21, 105, 2021.5.
24. Kinjo M, Nakamura Y, Taguchi S, Yamaguchi T, Tambo M, Okegawa T, Fukuhara H. Sex Differences in Prevalence and Patient Behavior Regarding Lower Urinary Tract Symptoms Among Japanese Medical Checkup Examinees. Urology, 151, 24-30, 2021.5.
25. COVID Surg Collaborative; Global Surg Collaborative. Timing of surgery following SARS-CoV-2 infection: an international prospective cohort study. Anaesthesia, 76(6), 748-758, 2021.6.
26. Kitamura T, Suzuki M, Shigehara K, Fukuda K. Prevalence and Risk Factors of Human Papillomavirus Infection among Japanese Female People: A Nationwide Epidemiological Survey by Self-Sampling. Asian Pac J Cancer Prev, 22(6), 1843-1849, 2021.6.
27. Manaka K, Sato J, Takeuchi M, Watanabe K, Kage H, Kawai T, Sato Y, Miyagawa T, Yamada D, Kume H, Sato S, Nagase T, Iiri T, Nangaku M and Makita N. Immune checkpoint inhibitor combination therapies very frequently induce secondary adrenal insufficiency. Scientific Reports, Open Access, 2021.6.
28. Fujii Y, Sato Y, Suzuki H, Kakiuchi N, Yoshizato T, Lenis A, Maekawa S, Yokoyama A, Takeuchi Y, Inoue Y, Ochi Y, Shiozawa S, Aoki K, Yoshida K, Kataoka K, Nakagawa M, Nannya Y, Makishima H, Miyakawa M, Kawai T, Morikawa T, Shiraishi K, Chiba K, Tanaka H, Nagae G, Sanada M, Sugihara E, Sato T, Nakagawa T, Fukayama M, Ushiku T, Aburatani H, Miyano S, Coleman J, Homma Y, Solit D, Kume H, Ogawa S. Molecular classification and diagnostics of upper urinary tract urothelial carcinoma. Cancer Cell, 39(6), 793-809, 2021.6.
29. Nakamura M, Ambe Y, Teshima T, Shirakawa N, Inatsu H, Amakawa R, Inoue Y, Yoshimatsu T, Imai S, Kusakabe M, Morikawa T, Kameyama S, Shiga Y. Assessment of surgical outcomes of off-clamp open partial nephrectomy without renorrhaphy for ≥T1b renal tumours. Int J Clin Oncol, Online ahead of print, 2021.6.
30. Dannno T, Iwata S, Niimi F, Honda S, Okada H, Azuma T. Nivolumab and Ipilimumab Combination Immunotherapy for Patients with Metastatic Collecting Duct Carcinoma. Nivolumab and Ipilimumab Combination Immunotherapy for Patients with Metastatic Collecting Duct Carcinoma, Open Access, 2021.6.
31. Takayama Ki, Kosaka T, Suzuki T, Hongo H, Oya M, Fujimura T, Suzuki Y, Inoue S. Subtype-specific collaborative transcription factor networks are promoted by OCT4 in the progression of prostate cancer. Nature Communications, 12, 3766, 2021.6.
32. Tohi Y, Kato T, Yokomizo A, Mitsuzuka K, Tomida R, Inokuchi J, Matsumoto R, Saito T, Sasaki H, Inoue K, Kinoshita H, Fukuhara H, Maruyama S, Sakamoto S, Tanikawa T, Egawa S, Ichikura H, Abe T, Nakamura M, Kakehi Y, Sugimoto M. Impact of health-related quality of life on repeat protocol biopsy compliance on active surveillance for favorable prostate cancer: results from a prospective cohort in the PRIAS-JAPAN study. Urol Oncol, Online ahead of print, 2021.6.
33. Kinno K, Sekido N, Takeuchi Y, Sawada Y, Watanabe S, Yoshimura Y. Association between overactive bladder and pelvic organ mobility as evaluated by dynamic magnetic resonance imaging. Sci. Rep, 11, 18148, 2021.7.
34. Uchihashi T, Nakahara H, Fukuhara H, Iwai M, Ito H, Sugauchi A, Tanaka M, Kogo M, Todo T. Oncolytic herpes virus G47Δ injected into tongue cancer swiftly traffics in lymphatics and suppresses metastasis. Mol Ther Oncolytics, 22, 388-398, 2021.7.

35. Kato T, Hirama H, Mitsuzuka K, Maruyama S, Sasaki H, Saito T, Matsumoto R, Sakamoto S, Sakai Y, Fukuhara H, Naya Y, Tsukino H, Hara I, Ogawa O, Hashine K, Fumimasa F, Yokomizo A, Tohi Y, Kakehi Y, Sugimoto M. Reclassification prediction of first-year protocol biopsy on active surveillance of prostate cancer by p2PSA-related parameters: from PRIAS-JAPAN. Prostate Cancer Prostatic Dis, Online ahead of print, 2021.7.
36. COVID Surg Collaborative; Global Surg Collaborative. SARS-CoV-2 infection and venous thromboembolism after surgery: an international prospective cohort study. Anaesthesia, Online ahead of print, 2021.8.
37. Wada K, Yokoyama T, Uno S, Araki M, Sadahira T, Maruyama Y, Acosta H, Nakajima H, Hiyama Y, Kunishima Y, Togo Y, Nukaya T, Yamada H, Shigemura K, Ito S, Tanimura M, Kobayashi K, Kitano H, Teishima J, Yasuda M, Watanabe T, Nakagawa T, Hayami H, Miyazaki J, Takahashi S, Masumori N, Ishikawa K, Kiyota H, Fujisawa M, Arakawa S, Nasu Y, Yamamoto S. Nationwide surveillance of bacterial pathogens isolated from patients with acute uncomplicated cystitis in 2018: conducted by the Japanese Research Group for Urinary Tract Infections (JRGU). J Infect Chemother, 27(8), 1169-1180, 2021.8.
38. Taguchi S, Kawai T, Nakagawa T, Nakamura Y, Kamei J, Obinata D, Yamaguchi K, Kaneko T, Kakutani S, Tokunaga M, Uemura Y, Sato Y, Fujimura T, Fukuhara H, Enomoto Y, Nishimatsu H, Takahashi S, Kume H. Prognostic significance of the albumin-to-globulin ratio for advanced urothelial carcinoma treated with pembrolizumab: A multicenter retrospective study. Scientific Reports, 11(1), 15623, 2021.8.
39. Imai S, Nakamura M, Chujo S, Ooki R, Inoue Y, Horiuchi H, Morikawa T, Uchino K, Igarashi A, Shiga Y. Immune-related dermatitis during combined treatment with pembrolizumab and axitinib in a patient with metastatic renal cell carcinoma with stasis dermatitis: A case report. IJU Case Rep, Open Access, 2021.8.
40. Yamada D, Kawai T, Sato Y, Yamada Y, Akiyama Y, Miyakawa J, Takahashi S, Kume H. Trends in prostate cancer diagnosis during the COVID-19 crisis: A report from one high-volume Japanese center. GHM Open, 1(1), 28-30, 2021.8.
41. Uemura H, Matsushima H, Yokomizo A, Kobayashi K, Arai G, Satoh T, Grillo V, Chen Y, Singh S, Athene Ledesma D. Unmet needs in non-metastatic castraton-resistant prostate cancer from the Japaneses patient perspective: a discrete choicec experiment. BMJ Open, 11(8), 2021.8.
42. Fukuhara H, Takeshima Y, Todo T. Triple-mutated oncolytic herpes virus for treating both fast- and slow-growing tumors. Cancer Sci, 112(8), 3293-3301, 2021.8.
43. Oshina T, Taguchi S, Miyakawa J, Akiyama Y, Sato Y, Kawai T, Fukuhara H, Nakagawa T, Kume H. Clinicopathological features and oncological outcomes of urothelial carcinoma involving the ureterovesical junction. Jpn J Clin Oncol, Online ahead of print, 2021.9.
44. Hagiwara K, Sakamoto A, Sasaki K, Kanatani A, Kimura M, Kaneko T, Takahashi S, Yamada Y, Nakagawa T. Higher serum alkaline phosphatase value indicates the need for bone mineral density testing in non-metastatic prostate cancer patients undergoing androgen deprivation therapy. Jpn J Clin Oncol, Online ahead of print, 2021.9.
45. COVID Surg Collaborative; Global Surg Collaborative. SARS-CoV-2 vaccination modelling for safe surgery to save lives: data from an international prospective cohort study. Br J Surg, 108(9), 1056-1063, 2021.9.
46. Takayama T, Fujita A, Sugihara T, Fujisaki A, Yamazaki M, Kameda T, Kamei J, Ando S, Kurokawa S, Fujimura T. Natural history of asymptomatic renal artery pseudoaneurysm after robot-assisted partial nephrectomy. Transl Androl Urol, 10(9), 3555-3565, 2021.9.
47. Kinjo M, Tanba M, Masuda K, Nakamura Y, Tanbo M, Fukuhara H. Comparison of effectiveness between modified transvaginal mesh surgery and vaginal pessary treatment in patients with symptomatic pelvic organ prolapse. Low Urin Tract Symptoms, Online ahead of print, 2021.9.
48. Kitamura J, Taguchi S, Okegawa T, Honda K, Kii T, Tomida Y, Matsumoto R, Ninomiya N, Masuda K, Nakamura Y, Yamaguchi T, Kinjo M, Tambo M, Isomura A, Hayashi A, Kamma H,

Higashihara E, Shibahara J, Fukuhara H. Genomic analysis of circulating tumor cells in adenosquamous carcinoma of the prostate: a case report. BMC Med Genomics, 14(1), 217, 2021.9.

49. Shigemori K, Higashihara E, Itoh M, Yoshida H, Yamamoto K, Nutahara K, Shiokawa Y, Kaname S, Tambo M, Yamaguchi T, Taguchi S, Yoshioka T, Yokoyama K, Fukuhara H. PKD1-Associated Arachnoid Cysts in Autosomal Dominant Polycystic Kidney Disease. J Stroke Cerebrovasc Dis, 30(9), 105943, 2021.9.
50. Sakaguchi K, Hayashida M, Tanaka N, Oka S, Urakami S. sk model for detecting clinically significant prostate cancer based on bi-parametric magnetic resonance imaging in a Japanese cohort. Scientific Reports, 11(1), 18829, 2021.9.
51. Kinoshita Y, Katano S, Nishida S, Shimizu T, Fujimura T, Kume H, Iwami D. Creatinine reduction ratio on postoperative day 2 predicts long-term outcomes after living donor kidney transplantation. Int J Urol, Online ahead of print, 2021.10.
52. Jimba M, Matsuzawa Y, Suzuki M, Kitamura T, Carandang R, Sieber N. Risk of increasing the sudden diagnosis of AIDS in Japan during and after COVID-19 outbreak. JMA Journal, Online ahead of print, 2021.10.
53. Akiyama Y, Niimi A, Igawa Y, Nomiya A, Yamada Y, Sato Y, Kawai T, Yamada D, Kume H, Homma Y. Cystectomy for patients with Hunner type interstitial cystitis at a tertiary referral center in Japan. Low Urin Tract Symptoms. Low Urinary Tract Symptoms, Online ahead of print, 2021.10.
54. Yamada Y, Nakagawa T, Miyakawa J, Kawai T, Tabata M, Kaneko T, Taguchi S, Naito A, Hikatsu M, Sato Y, Murata T, Matsumoto A, Miyazaki H, Suzuki M, Enomoto Y, Nishimatsu H, Kondo Y, Takeuchi T, Tanaka Y, Kume H. Smaller decline of renal function after nephroureterectomy predicts poorer prognosis of upper tract urothelial carcinoma: a multicentre retrospective study. Jpn J Clin Oncol, 51(10), 1577-1586, 2021.10.
55. Kamei J, Fujisaki A, Saito K, Sugihara T, Ando S, Miyagawa T, Takayama T, Fujimura T. Less invasive and equivalent short-term outcomes with simultaneous en bloc robot-assisted radical cystectomy and laparoscopic nephro-ureterectomy: Comparison with conventional open radical cystectomy and nephroureterectomy. Asian J Endosc Surg, Online ahead of print, 2021.10.
56. Tohi Y, Kato T, Nakamura M, Matsumoto R, Sasaki H, Mitsuzuka K, Inokuchi J, Hashine K, Yokomizo A, Naito H, Hara I, Kawamura N, Inoue M, Fukuhara H, Maruyama S, Sakamoto S, Saito T, Egawa S, Kakehi Y, Sugimoto M. Deferred radical prostatectomy in patients who initially elected for active surveillance: a multi-institutional, prospective, observational cohort of the PRIAS-JAPAN study. Int J Clin Oncol, Online ahead of print, 2021.10.
57. Ando S, Kamei J, Yamazaki M, Sugihara T, Kameda T, Fujisaki A, Kurokawa S, Takayama T, Fujimura T. Longer preserved urethral length in robot-assisted radical prostatectomy significantly contributes to post-operative urinary continence recovery. BJUI Compass, Online ahead of print, 2021.11.
58. COVID Surg Collaborative; Global Surg Collaborative. Effects of pre-operative isolation on postoperative pulmonary complications after elective surgery: an international prospective cohort study. Anaesthesia, 6(11), 1545-1464, 2021.11.
59. Nomura, Y., Okada, Y., Hiramatsu, A., Matsubara, E., Kato, K., Yoshimura, Y. A new method of adjusting mesh tension using cystoscopy during laparoscopic sacrocolpopexy. Int Urogynecology Journal, 32(11), 3089-3093, 2021.11.
60. Akiyama Y, Miyakawa J, O'Donnell MA, Kreder KJ, Luo Yi, Maeda D, Ushiku T, Kume H, Homma Y. Overexpression of HIF1α in Hunner Lesions of Interstitial Cystitis: Patho-physiological Implications. J Urol, Online ahead of print, 2021.11.
61. Yokomizo A, Yonese J, Egawa S, Fukuhara H, Uemura H, Nishimura K, Nagata M, Saito A, Lee T, Yamaguchi S, Nonomura N. Real-world use of enzalutamide in men with nonmetastatic castration-resistant prostate cancer in Japan. Int J Clin Oncol, Online ahead of print, 2021.11.
62. Fujisaki A, Takayama T, Teratani T, Kubo T, Kamei J, Sugihara T, Ando S, Morita T, Fujimura

T. Histological and radiological evaluation of thermal denaturation depth using soft coagulation during partial nephrectomy in living pigs. Int J Urol, 28(12), 1274-1280, 2021.12.

63. Higashihara E, Nutahara K, Itoh M, Okegawa T, Tambo M, Yamaguchi T, Nakamura Y, Taguchi S, Kaname S, Yokoyama K, Yoshioka T, Fukuhara H. Long-term outcomes of longitudinal efficacy study with tolvaptan in autosomal dominant polycystic kidney disease. Kidney International Reports, 7(2), 270-281, 2021.12.

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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, two Associate Professor, one Lecturers and nine 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), and preoperative chemoradiotherapy 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 555 surgically treated inpatients in the year of 2021. 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 chemo-therapeutic 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. Arakawa T, Ishihara S. Omental Endometriosis. The New England journal of medicine. 2021; 384(7):e21.
2. Emoto S, Hata K, Nozawa H, Kawai K, Tanaka T, Nishikawa T, et al. Risk factors for non-reaching of ileal pouch to the anus in laparoscopic restorative proctocolectomy with handsewn anastomosis for ulcerative colitis. Intest Res. 2021.
3. Fukui R, Nozawa H, Hirata Y, Kawai K, Hata K, Tanaka T, et al. Low preoperative maximum squeezing pressure evaluated by anorectal manometry is a risk factor for non-reversal of diverting stoma. Langenbecks Arch Surg. 2021; 406(1):131-9.
4. Fukui R, Sasaki K, Kawai K, Taira T, Nozawa H, Kaneko M, et al. Establishing a novel method for assessing elasticity of internal anal sphincter using ultrasonic real-time tissue elastography. ANZ journal of surgery. 2021;91(6):E360-e6.
5. Harada Y, Kazama S, Morikawa T, Sonoda H, Ishi H, Emoto S, et al. Clinical significance of CD8(+) and FoxP3(+) tumor-infiltrating lymphocytes and MFG-E8 expression in lower rectal cancer with preoperative chemo-radiotherapy. Molecular and clinical oncology. 2021;14(5):87.
6. Hojo D, Kawai K, Murono K, Nozawa H, Hata K, Tanaka T, et al. Establishment of deformable three-dimensional printed models for laparo-scopic right hemicolectomy in transverse colon cancer. ANZ journal of surgery. 2021;91(7-8): E493-e9.
7. Hojo D, Murono K, Nozawa H, Kawai K, Hata K, Tanaka T, et al. Improvement in Surgical Outcomes Using 3D Printed Models for Lateral Pelvic Lymph Node Dissection in Rectal Cancer. Dis Colon Rectum. 2021.
8. Iida T, Murono K, Shiratori H, Nozawa H, Kawai K, Sasaki K, et al. Impact of Inferior Mesenteric Artery Occlusion on the Calibre of Collateral Arteries of the Colon. Anticancer research. 2021; 41(10):5189-93.
9. Inagaki Y, Kawai K, Nishikawa T, Ishii H, Emoto S, Murono K, et al. Analysis of the Positional Relationship Among the Operator, Camera, and Monitor: Overcoming the Difficulties of Mirror-image Conditions During Laparoscopic Surgery. Surgical laparoscopy, endoscopy & percutaneous techniques. 2021.
10. Inoue H, Sasaki K, Nozawa H, Kawai K, Murono K, Emoto S, et al. Therapeutic significance of D3 dissection for low rectal cancer: a comparison of dissections between the lateral pelvic lymph nodes and the lymph nodes along the root of the inferior mesenteric artery in a multicenter retrospective cohort study. Int J Colorectal Dis. 2021;36(6):1263-70.
11. Ishimaru K, Kawai K, Nozawa H, Sasaki K, Murono K, Emoto S, et al. Hazard function analysis of metastatic recurrence after colorectal cancer surgery-A nationwide retrospective study. Journal of surgical oncology. 2021;123(4):1015-22.
12. Kamada Y, Hida K, Yonemura Y, Sugarbaker PH, Ghabra S, Ishihara S, et al. The Characteristics of 206 Long-Term Survivors with Peritoneal Metastases from Colorectal Cancer Treated with Curative Intent Surgery: A Multi-Center Cohort from PSOGI. Cancers (Basel). 2021;13(12).
13. Kaneko M, Nozawa H, Rokutan H, Murono K, Ushiku T, Ishihara S. Ectopic decidua of the appendix: a case report. Surgical case reports. 2021;7(1):117.
14. Kawai K, Nozawa H, Hata K, Tanaka T, Nishikawa T, Sasaki K, et al. Classification of the colonic splenic flexure based on three-dimensional CT analysis. BJS open. 2021;5(1).
15. Kawai K, Nozawa H, Sasaki K, Murono K, Ishihara S. Hazard function analysis for development of second primary colorectal cancer after surgery for primary colorectal cancer. Journal of gastroenterology and hepatology. 2021.
16. Kawai K, Shiratori H, Hata K, Nozawa H, Tanaka T, Nishikawa T, et al. Optimal Size Criteria for Lateral Lymph Node Dissection After Neoadjuvant Chemoradiotherapy for Rectal Cancer. Dis Colon Rectum. 2021;64(3):274-83.
17. Kitamura C, Sonoda H, Anzai H, Nagai Y, Abe S, Yokoyama Y, et al. Expression of Lyso-phosphatidylinositol Signaling-relevant Molecules

in Colorectal Cancer. Anticancer research. 2021; 41(5):2349-55.
18. Kobayashi T, Ikeda M, Ohama Y, Murono K, Ikeuchi K, Kitaura S, et al. First human case of catheter-related blood stream infection caused by Staphylococcus schleiferi subspecies coagulans: a case report and literature review. Ann Clin Microbiol Antimicrob. 2021;20(1):68.
19. Kokudo T, Saiura A, Takayama T, Miyagawa S, Yamamoto J, Ijichi M, et al. Adjuvant chemotherapy can prolong recurrence-free survival but did not influence the type of recurrence or subsequent treatment in patients with colorectal liver metastases. Surgery. 2021.
20. Miyake H, Kawai K, Nozawa H, Sasaki K, Kaneko M, Murono K, et al. Less intensive surveillance after radical surgery for stage I-III colorectal cancer by focusing on the doubling time of recurrence. Surg Today. 2021;51(4):550-60.
21. Murai S, Kawai K, Sonoda H, Nozawa H, Sasaki K, Murono K, et al. Computed tomographic colonography versus double-contrast barium enema for the preoperative evaluation of rectal cancer. Surg Today. 2021.
22. Murono K, Nozawa H, Kawai K, Sasaki K, Emoto S, Kishikawa J, et al. Vascular anatomy of the splenic flexure: a review of the literature. Surg Today. 2021.
23. Nozawa H, Emoto S, Sonoda H, Kawai K, Sasaki K, Kaneko M, et al. Liver Injury Among Japanese Patients Treated Using Prophylactic Enoxaparin After Colorectal Surgery. Dig Dis Sci. 2021;66(8):2805-15.
24. Nozawa H, Ishizawa T, Yasunaga H, Ishii H, Sonoda H, Emoto S, et al. Open and/or laparoscopic one-stage resections of primary colorectal cancer and synchronous liver metastases: An observational study. Medicine. 2021;100(11):e25205.
25. Nozawa H, Kawai K, Sasaki K, Murono K, Emoto S, Yokoyama Y, et al. Women are predisposed to early dose-limiting toxicities during adjuvant CAPOX for colorectal cancer. Int J Clin Pract. 2021:e14863.
26. Ochiai K, Kawai K, Nozawa H, Sasaki K, Kaneko M, Murono K, et al. Prognostic Impact and Clinicopathological Features of Multiple Colorectal Cancers and Extracolorectal Malignancies: A Nationwide Retrospective Study. Digestion. 2021:1-10.
27. Ochiai K, Kobayashi E, Tsukihara H, Nozawa H, Kawai K, Sasaki K, et al. Stereotactic Navigation System for Laparoscopic Lateral Pelvic Lymph Node Dissection. Dis Colon Rectum. 2021;64(6): e372-e7.
28. Okada M, Kawai K, Sonoda H, Shiratori H, Kishikawa J, Nagata H, et al. Epithelial-mesenchymal transition and metastatic ability of CD133(+) colorectal cancer stem-like cells under hypoxia. Oncology letters. 2021;21(1):19.
29. Okada S, Hata K, Shinagawa T, Noguchi T, Tanaka T, Kawai K, et al. A Polymorphism in Interleukin-1β Gene Is Associated with the Development of Pouchitis in Japanese Patients with Ulcerative Colitis. Digestion. 2021;102(3): 489-98.
30. Okamoto K, Emoto S, Sasaki K, Nozawa H, Kawai K, Murono K, et al. Extended Left Colectomy with Coloanal Anastomosis by Indocyanine Green-guided Deloyers Procedure: A Case Report. J Anus Rectum Colon. 2021;5(2): 202-6.
31. Okamoto K, Nozawa H, Hongo K, Iida Y, Kawai K, Sasaki K, et al. Risk factors of mFOLFOX6-induced hyperammonemia in patients with colorectal cancer: an observational study. International journal of clinical oncology. 2021; 26(8):1477-84.
32. Ozaki K, Kawai K, Nozawa H, Sasaki K, Murono K, Emoto S, et al. Therapeutic effects and limitations of chemoradiotherapy in advanced lower rectal cancer focusing on T4b. Int J Colorectal Dis. 2021;36(7):1525-34.
33. Ozaki K, Kawai K, Nozawa H, Sasaki K, Murono K, Ishihara S. Development of a novel apoptosis-based tumor regression grade to assess the efficacy of preoperative chemoradiotherapy for rectal cancer: a retrospective single-center study. International journal of clinical oncology. 2021;26(9):1679-88.
34. Ozawa T, Hashiguchi Y, Ishihara S, Hayama T, Tsuchiya T, Nozawa K, et al. Proposal for a post-operative surveillance strategy for stage I

colorectal cancer patients based on a novel recurrence risk stratification: a multicenter retrospective study. Int J Colorectal Dis. 2021; 36(1):67-74.

35. Ozawa T, Matsuda K, Ishihara S, Fukushima Y, Shimada R, Hayama T, et al. The robust performance of carcinoembryonic antigen levels after adjuvant chemotherapy for the recurrence risk stratification in patients with colorectal cancer. Journal of surgical oncology. 2021; 124(1):97-105.
36. Saito H, Tanimoto T, Ozawa T, Ishihara S, Fujishiro M, Shichijo S, et al. Automatic anatomical classification of colonoscopic images using deep convolutional neural networks. Gastroenterol Rep (Oxf). 2021;9(3):226-33.
37. Sakamoto A, Nozawa H, Sonoda H, Hinata M, Ishii H, Emoto S, et al. Rectal neuroendocrine tumor with extracapsular lymph node metastasis: a case report. Clinical journal of gastroenterology. 2021.
38. Sasaki K, Nozawa H, Kawai K, Murono K, Emoto S, Kishikawa J, et al. Risk of extracolonic malignancies and metachronous rectal cancer after colectomy and ileorectal anastomosis in familial adenomatous polyposis. Asian journal of surgery / Asian Surgical Association. 2021.
39. Sasaki K, Yoshimi F, Kawasaki H, Hayashi H, Hiyoshi M, Nagai H, et al. Usefulness of the gracilis muscle flap for reconstruction of large perineal defects following total pelvic exenteration with sacrectomy. ANZ journal of surgery. 2021;91(9):1932-4.
40. Tachikawa Y, Nozawa H, Hata K, Abe H, Ushiku T, Ishihara S. Metachronous ileal cancer after surgery for ascending colon cancer in a patient with Lynch syndrome: A case report. International journal of surgery case reports. 2021;81: 105714.
41. Tachikawa Y, Nozawa H, Otani K, Emoto S, Sonoda H, Mori K, et al. Definition and characterization of the descending branch of the left colic artery. Abdom Radiol (NY). 2021; 46(7):2993-3001.

Department of Vascular Surgery

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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 four 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 arterio-sclerosis.
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. Okata S, Hoshina K, Miyahara K, Matsukura M, Akai T, Isaji T, Takayama T. Highaneurysm wall enhancement values are associated with late sac shrinkage afterendovascular repair of abdominal aortic aneurysms. Medicine(Baltimore) 2021 Jan15;100:e24133.
2. Hoshina K, Kato M, Ishimaru S, Michihata N, Yasunaga H, Komori K; JapaneseCommittee for Stentgraft Management (JACSM). Impact of the urgency and the landingzone on rates of in-hospital death, stroke, and paraplegia following thoracic endovascularaortic repair in Japan. J Vasc Surg 2021; S0741-5214(21)00142-7.
3. 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.
4. Hoshina K, Komori K, Kumamaru H, Shimizu H. The Outcomes of EndovascularAneurysm Repair in Japan in 2017: A Report from the Japanese Committee for StentgraftManagement. 2021;25; 14:92-98.
5. Sugawara M, Hoshina K, Chigira M, Suzuki H, Daimon M, TakayamaT, Ono Y, Yatomi Y. Usefulness of duplex ultrasonography to detect collagen sponge misplacementinto the arterial lumen during the use of Angio-Seal: A case report. SAGE Open Med CaseRep 2021;9: 2050313X211004818
6. Matsuura S, Takayama T, Oyama TG, Oyama K, Taguchi M, Endo T, Akai T, IsajiT, Hoshina K. A Radiation-Crosslinked Gelatin Hydrogel That Promotes TissueIncorporation of an Expanded Polytetrafluoroethylene Vascular Graft in Rats. Biomolecules 2021;11:1105.
7. Iida T, Murono K, Shiratori H, Nozawa H, Kawai K, Sasaki K, Emoto S, KishikawaJ, 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 CollateralArteries of the Colon. Anticancer Res 2021;41:5189-5193.
8. Hoshina K, Komori K, Kumamaru H, Shimizu H. Theoutcomes of thoracicendovascular aortic repair in Japanin 2017: A report from the Japanese Committee forStentgraft Management. Ann Vasc Dis2021;14:281-288.111.
9. 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 GuidelineCommittee Japanese Society of Phlebology, Ogawa T, on behalf of Guideline Committeeof Endovenous Treatment for Varicose Veins. Supplement of clinical practice guidelinesfor endovenous thermal ablation for varicose veins: Overuse for the inappropriateindication. Ann Vasc Dis 2021:14: 323-327.

Department of Breast and Endocrine Surgery

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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. Sato A, Tanabe M, Tsuboi Y, Niwa T, Shinozaki-Ushiku A, Seto Y, Murakami Y. Circulating Tumor DNA Harboring the BRAFV600E Mutation May Predict Poor Outcomes of Primary Papillary Thyroid Cancer Patients. Thyroid. 2021 Dec;31(12):1822-1828.
2. 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.
3. Otsuji K, Sasaki T, Tanabe M, Seto Y. Quantitative assessment of HER2 gene amplification of breast cancer using droplet digital PCR. Pathol Int. 2021 Aug;71(8):538-547.
4. Konishi T, Fujiogi M, Michihata N, Morita K, Matsui H, Fushimi K, Tanabe M, Seto Y, Yasunaga H. Comparisons of postoperative outcomes after breast cancer surgery in patients with and without renal replacement therapy: a matched-pair cohort study using a Japanese nationwide inpatient database. Breast Cancer. 2021 Sep;28(5):1112-1119.
5. Konishi T, Fujiogi M, Michihata N, Kumazawa R, Matsui H, Fushimi K, Tanabe M, Seto Y, Yasunaga H. Outcomes of Nonoperative Treatment for Gastroduodenal Ulcer Perforation: a Nationwide Study of 14,918 Inpatients in Japan. J Gastrointest Surg. 2021 Nov;25(11):2770-2777.
6. Morizono A, Tanabe M, Ikemura M, Sasaki T, Ushiku T, Seto Y. Loss of BRCA1 expression and morphological features associated with BRCA1 promoter methylation status in triple-negative breast cancer. J Hum Genet. 2021 Aug;66(8): 785-793.
7. Konishi T, Fujiogi M, Michihata N, Morita K, Matsui H, Fushimi K, Tanabe M, Seto Y, Yasunaga H. Comparison of short-term surgical outcomes between men and women with breast cancer: a retrospective study using nationwide inpatient data in Japan. Breast Cancer Res Treat. 2021 Apr;186(3):731-739.
8. Konishi T, Fujiogi M, Michihata N, Morita K, Matsui H, Fushimi K, Tanabe M, Seto Y, Yasunaga H. Comparing outcomes of nonoperative treatment for adhesive small bowel obstruction with and without antibiotics. J Infect Chemother. 2021 May;27(5):690-695.
9. Murayama T, Takeuchi Y, Yamawaki K, Natsume T, Li M, Marcela RN, Nishimura T, Kogure Y, Nakata A, Tominaga K, Sasahara A, Yano M, Ishikawa S, Ohta T, Ikeda K, Horie-Inoue K, Inoue S, Seki M, Suzuki Y, Sugano S, Enomoto T, Tanabe M, Tada KI, Kanemaki MT, Okamoto K, Tojo A, Gotoh N. MCM10 compensates for Myc-induced DNA replication stress in breast cancer stem-like cells. Cancer Sci. 2021 Mar; 112(3):1209-1224.

Surgical Sciences

2. Sensory and Motor System Medicine

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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.

The professor, two associate professors, four lecturers, one hospital lecturer 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, eight 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. Miura S, Watanabe Y, Saigusa R, Yamashita T, Nakamura K, Hirabayashi M, Miyagawa T, Yoshizaki A, Trojanowska M, Sato S, Asano Y. Fli1 deficiency suppresses RALDH1 activity of dermal dendritic cells and related induction of regulatory T cells: a possible role in scleroderma. Arthritis Res Ther. 2021;23(1):137.
2. Awaji K, Miyagawa T, Omatsu J, Numajiri H, Kawai T, Funamizu K, Saigusa R, Yamada D, Asano Y, Sato S.The prognostic relevance of pretreatment peripheral neutrophil counts and neutrophil-to-lymphocyte ratio in primary cutaneous angiosarcoma. Acta Dermato Venereol. 2021;101(8):adv00527.
3. Minami Sakamoto, Tomomitsu Miyagaki, Hiroaki Kamijo, Tomonori Oka, Hikari Boki, Naomi Takahashi-Shishido, Hiraku Suga, Makoto Sugaya, Shinichi Sato. CD147-cyclophilin A interactions promote proliferation and survival of cutaneous T-cell lymphoma International. Int Journal of Molecular Sciences. 2021;22(15):7889.
4. Hayakazu Sumida, Kiyoshi Migita, Hiroaki Ida, Yoshihide Asano, Jun Shimizu, Shinji Kagami, Makoto Sugaya, Takafumi Kadono, Shinichi Sato. Dermatomyositis-like eruptions and fasciitis with novel compound heterozygous MEFV mutations: newly recognized features of a variant of familial Mediterranean fever. The Journal of Dermatology. 2021;48(9):1453-1456.
5. Shibata Sayaka. Chromatin dynamics and epigenetics in skin stress adaptation. The Journal of Dermatological Science. 2021;103(2):66-72.
6. Hikari Boki, Takayuki Kimura, Tomomitsu Miyagaki, Hiraku Suga, Andrew Blauvelt, Hitoshi Okochi, Makoto Sugaya, Shinichi Sato. Lymphatic dysfunction exacerbates cutaneous tumorigenesis and psoriasis-like skin inflammation through accumulation of inflammatory cytokines. Journal of Investigative Dermatology. 2022;142(6):1692-1702.
7. Hiroko Numajiri, Ai Kuzumi, Takemichi Fukasawa, Satoshi Ebata, Asako Yoshizaki-Ogawa, Yoshihide Asano, Yutaka Kazoe, Kazuma Mawatari, Takehiko Kitamori, Ayumi Yoshizaki, and Shinichi Sato. B cell depletion inhibits fibrosis via suppressing pro-fibrotic macrophage differentiation in a mouse model of systemic sclerosis. Arthritis & Rheumatology. 2021;73(11):2086-2095.
8. Ai Kuzumi, Ayumi Yoshizaki, Kazuki M Matsuda, Hirohito Kotani, Yuta Norimatsu, Maiko Fukayama, Satoshi Ebata, Takemichi Fukasawa, Asako Yoshizaki-Ogawa, Yoshihide Asano, Kyojiro Morikawa, Yutaka Kazoe, Kazuma Mawatari, Takehiko Kitamori, Shinichi Sato. Interleukin-31 promotes fibrosis and T helper 2 polarization in systemic sclerosis. Nature Communications. 2021;12(1):5947.
9. Ikawa T, Ichimura Y, Miyagawa T, Fukui Y, Toyama S, Omatsu J, Awaji K, Norimatsu Y, Watanabe Y, Yoshizaki A, Sato S, Asano Y. The contribution of LIGHT to the development of systemic sclerosis by modulating IL-6 and Th1 chemokine expression in dermal fibroblasts. J Invest Dermatol. 2022;142(6):1541-1551.
10. Satoshi Ebata, Ayumi Yoshizaki, Takemichi Fukasawa, Asako Yoshizaki-Ogawa, Yoshihide Asano, Kosuke Kashiwabara, Koji Oba, Shinichi

Sato. The Percentage of Residual B-Cells after 2 Weeks of Rituximab Treatment Predicts the Improvement of Systemic Sclerosis-associated Interstitial Lung Disease.The Journal of Dermatology. 2022;49(1):179-183.

11. Ikawa T, Miyagawa T, Fukui Y, Toyama S, Omatsu J, Awaji K, Norimatsu Y, Watanabe Y, Yoshizaki A, Sato S, Asano Y. Endothelial CCR6 expression due to FLI1 deficiency contributes to vasculopathy associated with systemic sclerosis.Arthritis Res Ther. 2021;23(1):283
12. Ai Kuzumi, Ayumi Yoshizaki, Kazue Chiba, Shunki Mitsuo, Kazuki M Matsuda, Yuta Norimatsu, Kojiro Nagai, Jun Omatsu, Tomomi Miyake, Shinichi Sato. Genital necrosis with cutaneous thrombosis after COVID-19 mRNA vaccination. Journal of The European Academy of Dermatology and Venereology. 2022;36(3): e185-e186.
13. Takemichi Fukasawa, Ayumi Yoshizaki, Satoshi Ebata, Asako Yoshizaki-Ogawa, Yoshihide Asano, Atsushi Enomoto, Kiyoshi Miyagawa, Yutaka Kazoe, Kazuma Mawatari, Takehiko Kitamori, Shinichi Sato. Single cell level protein analysis revealing the roles of autoantigen-reactive B lymphocytes in autoimmune disease and the murine model. eLife. 2021;10:e67209.
14. Yuki Kawana, Hiraku Suga, Hiroaki Kamijo, Tomomitsu Miyagaki, Makoto Sugaya, Shinichi Sato. Roles of OX40 and OX40 ligand in cutaneous T-cell lymphoma. International Journal of Molecular Sciences. 2021;22(22): 12576.
15. Mariko Urano-Takaoka, Hayakazu Sumida, Takuya Miyagawa, Kentaro Awaji, Kojiro Nagai, Jun Omatsu, Tomomi Miyake, Shinichi Sato. Serum Cytokeratin 18 as a Metastatic and Therapeutic Marker for Extramammary Paget's Disease. Acta Derm Venereol. 2022;102: adv00636.
16. Kazuki Mitsuru Matsuda, Ayumi Yoshizaki, Kei Yamaguchi, Eriko Fukuda, Taishi Okumura, Koji Ogawa, Chihiro Ono, Yuta Norimatsu, Hirohito Kotani, Teruyoshi Hisamoto, Ruriko Kawanabe, Ai Kuzumi, Takemichi Fukasawa, Satoshi Ebata, Takuya Miyagawa, Asako Yoshizaki-Ogawa, Naoki Goshima, Shinichi Sato. Autoantibody landscape revealed by wet protein array: sum of autoantibody levels reflects disease status. Frontiers in Immunology. 2022;13:893086.
17. Satoshi Ebata, Ayumi Yoshizaki, Koji Oba, Kosuke Kashiwabara, Keiko Ueda, Yukari Uemura, Takeyuki Watadani, Takemichi Fukasawa, Shunsuke Miura, Asako Yoshizaki-Ogawa, Naoko Okiyama, Masanari Kodera, Minoru Hasegawa, Shinichi Sato. Safety and efficacy of rituximab in systemic sclerosis (DESIRES): open-label extension of a double-blind, investigators-initiated, randomized, placebo-controlled trial. Lancet Rheumatology. 2021;3(7):e489-e497.
18. Ruriko Kawanabe, Ayumi Yoshizaki, Kazuki M. Matsuda, Hirohito Kotani, Teruyoshi Hisamoto, Yuta Norimatsu, Ai Kuzumi, Takemichi Fukasawa, Satoshi Ebata, Asako Yoshizaki-Ogawa and Shinichi Sato. Serum C-X-C chemokine ligand 1 levels in patients with systemic sclerosis: relationship of clinical and laboratory observations to anti-CD20 monoclonal antibody administration. Life. 2022;12(5):646.
19. Ayumi Yoshizaki, Shinichi Sato. Predictors of Rituximab Effect on Modified Rodnan Skin Score in Systemic Sclerosis: a machine learning analysis of the DESIRES trial. Rheumatology. in press.
20. 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. in press.

Department of Plastic and Reconstructive Surgery

Professor

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Organization

The present faculty of the Department of Plastic and Reconstructive Surgery consists of 1 professor, 1 associate professor, 2 project lecturers, 5 associates, 6 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 (2021)

1. Hidaka T, Ogawa K, Tomioka Y, Yoshii K, Okazaki M. The Impact of Brow-Lift on Eyelid Closure in Patients with Facial Paralysis. Facial Plast Surg Aesthet Med. 2021 Dec 3. doi: 10.1089/fpsam.2021.0120.
2. Tanaka K, Sugawara T, Asakage T, Okazaki M. A Concept of "Boundary Determination" by the Combination of a Local Flap and Free Tissue Transfer Useful for the Prevention of Postoperative Complications After Complex and Widespread Skull Base Reconstruction. J Craniofac Surg. 2021 Nov-Dec 01;32(8):e820-e822.
3. Yamashita S, Nakazato M, Hirata T. Size Analysis of Small Metal Nanoparticles Using Single Particle ICP Mass Spectrometry. Anal Sci. 2021 Nov 10;37(11):1637-1640.
4. Fujisawa K, Miyamoto S, Saito Y, Fukuoka O, Okazaki M. Total Maxillectomy and Free Flap Reconstruction in Hemodialysis Patients: Report of Two Cases. Plast Reconstr Surg Glob Open. 2021 Nov 4;9(11):e3922.
5. Hidaka T, Miyamoto S, Ogawa K, Tomioka Y, Okazaki M. Factors Associated With Late Admission to Facial Plastic Surgery Among Patients With Long-Standing Facial Paralysis. Ann Plast Surg. 2021 Nov 1;87(5):547-551.
6. Kanayama K, Oba J, Yoshii K, Tomioka Y, Kurita M, Miyamoto S, Okazaki M. Potentially serious incidental findings on medical imaging in plastic surgery patients: A single-institution retrospective cohort study. J Plast Reconstr Aesthet Surg. 2021 Oct;74(10):2776-2820.
7. Kato M, Kurita M, Mito D, Nakamura R, Li K, Yamashita S, Okazaki M. Establishing a Lymphatic Venous Anastomotic Training Model in Pig Trotters. J Reconstr Microsurg. 2021 Oct; 37(8):682-686.
8. Kanayama K, Kato H, Mori M, Sakae Y, Okazaki M. Robotically Assisted Recipient Site Preparation in Hair Restoration Surgery: Surgical Safety and Clinical Outcomes in 31 Consecutive Patients. Dermatol Surg. 2021 Oct 1;47(10): 1365-1370.
9. Kagaya Y, Arikawa M, Akazawa S, Miyamoto S. A Quantitative Evaluation of the Flow-Increasing Effect of Flow-Through Arterial Anastomosis in the Vascular Pedicle of Free Flaps: A Prospective Clinical Before-and-After Study. Plast Reconstr Surg. 2021 Oct 1;148(4):871-881.
10. Ogawa K, Okazaki M, Tanaka K, Uemura N, Homma T. Chimeric Latissimus Dorsi Flap in One-Stage Reconstruction of Depressor Muscle Dysfunction and Depression Deformity in the Perimandibular Area. J Craniofac Surg. 2021 Oct 1;32(7):2512-2515.
11. Yoshida S, Koshima I, Imai H, Uchiki T, Sasaki A, Fujioka Y, Nagamatsu S, Yokota K, Yamashita S. Modified intraoperative distal compression method for lymphaticovenous anastomosis with high success and a low venous reflux rates. J Plast Reconstr Aesthet Surg. 2021 Sep;74(9): 2050-2058.
12. Moriwaki Y, Kurita M, Hongo H, Okazaki M. In Vitro Comparative Cytotoxicity Assessment of Sclerosants Used for Venous Malformations.

Plast Reconstr Surg Glob Open. 2021 Sep 17; 9(9):e3814.
13. Kagaya Y, Arikawa M, Sekiyama T, Mitsuwa H, Takanashi R, Taga M, Akazawa S, Miyamoto S. The concept of "whole perforator system" in the lateral thoracic region for latissimus dorsi muscle-preserving large flaps: An anatomical study and case series. PLoS One. 2021 Sep 2; 16(9):e0256962.
14. Iida T, Isozaki Y, Numahata T, Okazaki M. Sacral defect reconstruction using a sensate superior gluteal artery perforator flap based on the superior cluneal nerves: A report of two cases. Microsurgery. 2021 Jul;41(5):468-472.
15. Miyamoto S, Arikawa M, Kagaya Y. Response to letter commenting on "The use of lower abdominal perforator flaps in soft-tissue reconstruction after sarcoma resection". Microsurgery. 2021 May;41(4):396-397.
16. Hidaka T, Yamashita S, Okazaki M. A Possible Distal End for Perforasome of the Superficial Circumflex Iliac Artery Perforator Flap. Plast Reconstr Surg Glob Open. 2021 May 28;9(5): e3602.
17. Ogawa K, Okazaki M, Tanaka K, Uemura N, Homma T. One-Stage Simultaneous Augmentation of 2 Regions of 3 Facial Reanimations After Mid Skull Base Surgery by Using a Neurovascular Latissimus Dorsi Chimeric Flap. J Craniofac Surg. 2021 Mar-Apr 01;32(2):730-733.
18. Roh S, Miyamoto S, Kitamura Y, Mito D, Okazaki M. Secondary Vulvar Reconstruction Using Bilateral Gluteal Fold Flaps after Radical Vulvectomy with Direct Closure. Plast Reconstr Surg Glob Open. 2021 Apr 20;9(4):e3550.
19. Hattori Y, Kurita M, Yokoyama T, Yamashita S, Okazaki M. Arteriovenous Malformation of the Head and Neck in a Hemodialysis Patient. Plast Reconstr Surg Glob Open. 2021 Mar 24;9(3): e3485.
20. Mashiko T, Kanayama K, Saito N, Shirado T, Asahi R, Mori M, Yoshimura K. Selective Proliferation of Highly Functional Adipose-Derived Stem Cells in Microgravity Culture with Stirred Microspheres. Cells. 2021 Mar 4;10(3): 560.
21. Miyamoto S, Kageyama D, Arikawa M, Kagaya Y, Fukunaga Y. Combined use of ipsilateral latissimus dorsi flap and anterolateral thigh flap to reconstruct extensive trunk defects. Microsurgery. 2021 Feb;41(2):175-180.
22. Fujisawa K, Ito T, Aoyama S, Kiuchi T, Araki J, Nakao J, Nakagawa M. Thorax anthropometric position index: a simple evaluation of the inframammary fold position in the thorax. J Plast Surg Hand Surg. 2021 Feb;55(1):21-24.
23. Matsumoto M, Nakagami G, Kitamura A, Kurita M, Suga H, Miyake T, Kawamoto A, Sanada H. Ultrasound assessment of deep tissue on the wound bed and periwound skin: A classification system using ultrasound images. J Tissue Viability. 2021 Feb;30(1):28-35.
24. Fujisawa K, Kitatsuji M, Yamamoto Y. Open Abdomen Negative Pressure Device Applied for Two-stage Closure of Enterocutaneous Fistula. Plast Reconstr Surg Glob Open. 2021 Feb 1;9(2): e3369.
25. Kagaya Y, Arikawa M, Higashino T, Miyamoto S. Letter of response to comments on publication: "Autologous abdominal wall reconstruction using anterolateral thigh and iliotibial tract flap after extensive tumor resection: A case series study of 50 consecutive cases". J Plast Reconstr Aesthet Surg. 2021 Jan;74(1):223-243.
26. Matsutani Hitomi, Kamochi Hideaki, Ishikawa Yohei. Use of Surgical Tape Strips to Eliminate Hair Fragments from Split-thickness Skin Grafts from the Scalp:A Simple and Quick Technique. International Journal of Surgical Wound Care, 2(1) 32-35, 2021.

Department of Oral-Maxillofacial Surgery

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Yoko Uchida, D.D.S., Ph.D.
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Miki Kashiwagi, D.D.S., Ph.D. (from July)

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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 chiloplasty 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 distraction 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. Mori T, Kumagai K, Nasu K, Yoshizawa T, Kuwano K, Hamada Y, Kanazawa H, Suzuki R. Clonal Expansion of Tumor-Infiltrating T Cells and Analysis of the Tumor Microenvironment within Esophageal Squamous Cell Carcinoma Relapsed after Definitive Chemoradiation Therapy. Int J Mol Sci. 2021 Jan 22; 22(3):1098. doi: 10.3390/ijms22031098.【査読有】
2. Koseki J, Abe T, Miyamoto Y, Kashiwagi M, Ishibashi M, Taniguchi A, Suenaga H, Abe H, Abe M, Hoshi K. Use of application of navigation system to odontogenic benign tumors with maxilla. Biomed Res, 2021; 32(2): 37-41, Accepted Feb 9, 2021 (Online)
3. Fujihara Y, Abe T, Asawa Y, Nishizawa S, Saijo H, Hikita A, Hoshi K. Influence of Damage-Associated Molecular Patterns from Chondrocytes in Tissue- Engineered Cartilage. Tissue Eng Part A. 2021 Jan; 27(1-2):1-9. doi: 10.1089/ten.TEA.2019.0185. Epub 2020 Feb 19. PMID: 31724485.【査読有】
4. Nakamura M, Hakozaki Y, Iwata S, Sato Y, Makino K, Kawai T, Yamada Y, Yamada D, Suzuki M, Omatsu J, Abe M, Hoshi K, Kume H, Igawa Y. Novel operative technique of advance-ment urethral meatoplasty utilizing buccal mucosa for Vulvar Paget's disease with urethral invasion, Case reports. Journal of Medical Case Reports. 2021 Mar 28; 15(1):136, doi: 10.1186/s13256-021-02729-1, PMID: 33773597, PMCID: PMC8005229, Free PMC Article.【査読有】
5. Abe M, Mitani A, Yao A, Zhang C, Hoshi K, Yanagimoto S. Awareness of Teeth-Alignment Disorder is Closely Associated with Gum Bleeding and Pollinosis in Late Adolescence. Healthcare. 9(4):370, 2021. Published 26 March, 2021 【査読有】

6. Kanata Tonosaki, Kazumichi Yonenaga, Tetsuhiko Mikami, Takashi Mizuno, Shigeto Oyama. Acute Cholecystitis, Sepsis, and Disseminated Intravascular Coagulation Caused by Edwardsiella tarda in an Elderly Woman. The Tokai journal of experimental and clinical medicine 46(1) 51-53 2021.4.20. PMID: 34859417.【査読有】
7. Kanata Tonosaki, Kazumichi Yonenaga, Sachiko Ono, Shunsuke Itai, Shigeto Oyama, Takashi Mizuno, Rinji Watanabe, Kazuto Hoshi. Swallowing evaluation by the Kuchikara Taberu Balance Chart and videoendscopic examination reveals that respiratory conditions, chewing, and position are strongly related to dysphagia. Odontology 109(2) 448-452 2021.Apr. Epub 2020 Oct 27. doi: 10.1007/s10266-020-00561-5. PMID: 33108554.【査読有】
8. Kanazawa S, Okada H, Hojo H, Ohba S, Iwata J, Komura M, Hikita A, Hoshi K. Mesenchymal stromal cells in the bone marrow niche consist of multi□populations with distinct transcriptional and epigenetic properties. Sci Rep. 2021 Aug 4;11(1):15811. doi: 10.1038/s41598-021-94186-5. PMID: 34349154 【査読有】
9. Ning F, N Zhang N, Wang J, Jin Y, Quan H, Pei J, Zhao Y, Zeng X, Abe M, Zhang C. Prognostic value of modified Lauren classification in gastric cancer. World Journal of Gastrointestinal Oncology. 13(9):1184-1195, 2021 Sep 15. 【査読有】
10. Miyamoto Y, Kubota K, Asawa Y, Hikita A, Hoshi K. M1-like macrophage contributes to chondrogenesis in vitro. Sci Rep, 2021 Oct 29, 11:21307 (Online), doi.org/10.1038/s41598-021-7 【査読有】
11. Pei J, Zhang R, Zhang N, Zeng Y, Sun Z, Ma S, Zhou J, Li X, Fan J, Zhu J, Abe M, Mei Z, Shi G, Zhang C. Screening and Validation of a Novel T Stage-Lymph Node Ratio Classification for Operable Colon Cancer. Annals of Translational Medicine. 9(20):1513, 2021.Oct. 【査読有】
12. Ono S, Abe T, Abe M, Kubota K, Hoshi K. Squamous cell carcinoma at the oral commissure in a patient with Behçet's disease. J Oral Maxillofac Surg Med Pathol, 2021 Nov;33(6): 610-613.【査読有】
13. Kanata Tonosaki, Kazumichi Yonenaga, Shunsuke Itai, Takashi Mizuno, Shigeto Oyama. Familial Mediterranean fever with psychiatric disorder which have not been diagnosed over 30 years: A case report. The Tokai Journal of Experimental and Clinical Medicine 46(4) 180-183 2021.12. PMID: 34859417.【査読有】

(Review articles)

1. Abe M, Mitani A, Zong L., Hoshi K, Yanagimoto S. The Challenge of Early Prevention of Periodontal Diseases in Japan. Journal of Advanced Oral Research, online, doi: 10.1177/ 23202068211022586, 2021 June. 【査読有】
2. Abe M, Mitani A, Zong L, Zhang C, Hoshi K, Yanagimoto S. High Frequency and Long Duration of Toothbrushing Can Potentially Reduce the Risk of Common Systemic Diseases in Late Adolescence. Special Care in Dentistry 42(3):317-318, 2022 May, Epub 2021 Oct 22 doi: 10.1111/scd.12670. 【査読有】
3. Hoshi K, Ikebe T, Ota Y, Kishimoto H, Kurata T, Kurita H, Sakamaki K, Takenobu T, Harada S, Ogasawara T, Tei K, Kirita T. Guide for Surgical Procedures in Oral And Maxillofacial Areas during Coronavirus Disease 2019 Pandemic. J Oral Maxillofac Surg Med Pathol. 2021 Oct 28. doi: 10.1016/j.ajoms.2021.10.007. Epub ahead of print. PMID: 34729347; PMCID: PMC8552586. 【査読有】

(Patents)

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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, four lecturers, 14 associates, nine medical staff members, and seven 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 8 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 36,291 patients visited the outpatient clinic in fiscal 2019.

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.

1,464 operations were performed in fiscal 2019. These include 364 spine surgeries, 73 surgeries for rheumatoid arthritis patients, 115 hip surgeries, 313 knee surgeries (including 31 computer-assisted ACL reconstructions, 140 computer-assisted TKA, 21 UKA), 237 hand surgeries, 52 foot and ankle surgeries, 44 pediatric surgeries, 153 surgeries for bone and soft tissue tumor, and 177 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.

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 chemotherapy, limb sparing surgery and radiotherapy in coorporation 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. Four 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, Division of Tissue Engineering. 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.

References

1. Shibayama K, Sugaya H, Matsuki K, Takahashi N, Tokai M, Onishi K, Tanaka S: Repair Integrity and Functional Outcomes After Arthroscopic Suture Bridge Subscapularis Tendon Repair. Arthroscopy 2018,34:2541-2548
2. Tanaka T, Takao M, Sakai T, Hamada H, Tanaka S, Sugano N: Variations in sagittal and coronal stem tilt and their impact on prosthetic impingement in total hip arthroplasty. Artif Organs 2018, Epub
3. Kawaguchi K, Michishita K, Manabe T, Akasaka Y, Arakawa T, Higuchi J: Mucoid degeneration of the cruciate ligaments in osteoarthritis under primary total knee arthroplasty. Asia-Pacific Journal of Sports Medicine, Arthroscopy, Rehabilitation and Technology 2018,12:1-4
4. Ono K, Hirose J, Chang SH, Kubota M, Kinkawa J, Noguchi M, Takedani H: Orthotropic live transplantation for cirrhosis from hepatitis C virus leads to correction of factor IX deficiency allowing for ankle arthroplasty without factor replacement in a patient with moderate haemophilia B. Blood Coagul Fibrinolysis 2018, 29(1): 131-134
5. Tsuda Y, Ogura K, Shinoda Y, Kobayashi H, Tanaka S, Kawai A: The outcomes and prognostic factors in patients with osteosarcoma according to age: a Japanese nationwide study with focusing on the age differences. BMC Cancer 2018, 18(1): 614
6. Oka H, Matsudaira K, Takano Y,Kasuya D, Niiya M, Tonosu J,Fukushima M, Oshima Y, Fujii T, Tanaka S, Inanami H: A comparative study of three conservative treatments in patients with lumbar spinal stenosis: lumbar spinal stenosis with acupuncture and physical therapy study (LAP study). BMC Complement Altern Med 2018, Jan 19;18(1)
7. Yamada K, Muranaga S, Shinozaki T, Nakamura K, Tanaka S, Ogata T: BMC Geriatr 2018, Jan 26; 18(1):28
8. Doi T, Inoue H, Arai Y, Shirado O, Doi T, Yamazaki K, Uno K, Yanagida H, Takeshita K: Reliability and validity of a novel quality of life questionnaire for female patients with adolescent idiopathic scoliosis: Scoliosis Japanese Questionnaire-27: a multicenter, cross-sectional study. BMC Musculoskelet Disord 2018,19(1):99
9. Fujii T, Oka H, Katsuhira J, Tonosu J, Kasahara S, Tanaka S, Matsudaira K: Disability due to knee pain and somatising tendency in Japanese adults. BMC Musculoskelet Disord 2018, Jan 19; 19(1): 23
10. Tonosu J, Inanami H, Oka H, Takano Y, Koga H, Yuzawa Y, Shiboi R, Oshima Y, Baba S, Tanaka S, Matsudaira K: Factors related to subjective satisfaction following microendoscopic foraminotomy for cervical radiculopathy. BMC Musculoskelet Disord 2018, Jan 24;19(1):30
11. Oshina M, Oshima Y, Matsubayashi Y, Taniguchi Y, Chikuda H, Riew KD, Tanaka S: Nutrient foramen location on the laminae provides a landmark for pedicle screw entry: a cadaveric study. BMC Musculoskelet Disord 2018, 19(1): 293
12. Omiya T, Hirose J, Hasegawa T, Amizuka N, Omata Y, Izawa N, Yasuda H, Kadono Y, Matsumoto M, Nakamura M, Miyamoto T, Tanaka S: The effect of switching from teriparatide to anti-RANKL antibody on cancellous and cortical bone in ovariectomized mice. Bone 2018,107: 18-26
13. Chang SH, Matsumoto T, Okajima K, Naito M, Hirose J, Tanaka S: Heterotopic Ossification of the Peroneus Longus Tendon in the Retromalleolar Portion with the Peroneus Quartus Muscle: A Case Report. Case Rep Orthop 2018, Jul 29
14. Kobayashi H, Ikegami M, Ushiku T, Anraku M, Ohki T, Shinoda Y, Tanaka S, Kawano H: Secondary Chondrosarcoma Presenting with Symptoms Similar to Thoracic Outlet Syndrome. Case Rep Orthop 2018, Mar 12
15. Matsumoto T, Chang SH, Takeda R, Tanaka S, Juji T: Bilateral Stress Fractures of the Talus Associated with Adult-Acquired Flatfoot Deformities. Case Rep Orthop 2018, Sep 9
16. Tanaka T, Ito H, Oshima H, Haga N, Tanaka S: Total Hip Arthroplasty in a Patient with Oto-Spondylo-Megaepiphyseal Dysplasia Planned by Three-Dimensional Motion Analyses and Full-Scale Three-Dimensional Plaster Model of Bones. Case Rep Orthop 2018, Jan 23

17. Omata Y, Frech M, Primbs T, Lucas S, Andreev D, Scholtysek C, Sarter K, Kindermann M, Yeremenko N, Baeten DL, Andreas N, Kamradt T: Group 2 Innate Lymphoid Cells Attenuate Inflammatory Arthritis and Protect from Bone Destruction in Mice 2018,24:169-180
18. Ogata T, Ideno Y, Akai M, Seichi A, Hagino H, Iwaya T, Doi T, Yamada K, Chen AZ, Li Y, Hayashi K: Effects of glucosamine in patients with osteoarthritis of the knee: a systematic review and meta-analysis. Clin Rheumatol 2018, 37(9):2479-2487
19. Oshina M, Horii C, Hirai S, Matsubayashi Y, Taniguchi Y, Hayashi N, Tanaka S, Oshima Y: Lewis SJ, Mohanty C, Gazendam AM, Kato S, Keshen SG, Lewis ND, Magana SP, Perlmutter D, Cape J: Posterior column reconstruction improves fusion rates at the level of osteotomy in three-column posterior-based osteotomies. Eur Spine J 2018, 27(3):636-643
20. Comparison of Freehand Sagittal Trajectories for Inserting Pedicle Screws Between C7) and T5. Clin Spine Surg 2018, 31(7):E357-E362
21. Ganau M, Kato S, Oshima Y: Letter to the Editor concerning "Osteoporotic thoracolumbar compression fractures: long-term retrospective comparison between vertebroplasty and conservative treatment" by K. Martikos et al. Eur Spine 2018, J 27(7):1662-1663
22. Oshina M, Tanaka M, Oshima Y, Tanaka S, Riew KD: Correlation and differences in cervical sagittal alignment parameters between cervical radiographs and magnetic resonance images. Eur Spine J 2018,27(6):1408-1415
23. Maenohara Y, Taniguchi A, Tomiwa K, Tsuboyama D, Kurokawa H, Kumai T, Tanaka S, Tanaka Y: Outcomes of Bilateral vs Unilateral Ankle Arthrodesis. Foot Ankle Int 2018,39:530-534
24. Matsumoto T, Gross CE, Parekh SG: Short-Term Radiographic Outcome After Distal Chevron Osteotomy for Hallux Valgus Using Intramedullary Plates With an Amended Algorithm for the Surgical Management of Hallux Valgus. Foot Ankle Spec 2018, Epub
25. Oshina M, Oshima Y, Tanaka S, Riew KD: Radiological Fusion Criteria of Postoperative Anterior Cervical Discectomy and Fusion: A Systematic Review. Global Spine J 2018, 8(7): 739-750
26. Lewis SJ, Keshen SG, Kato S, Dear TE, Gazendam AM: Risk Factors for Postoperative Coronal Balance in Adult Spinal Deformity Surgery. Global Spine J 2018, 8(7):690-697
27. Kobayashi H, Okuma T, Oka H, Okajima K, Ishibashi Y, Zhang L, Hirai T, Ohki T, Tsuda Y, Ikegami M, Sawada R, Shinoda Y, Akiyama T, Kawano H, Goto T, Tanaka S: Body composition as a predictor of toxicity after treatment with eribulin for advanced soft tissue sarcoma. Int J Clin Oncol 2018, Epub
28. Kobayashi H, Okuma T, Oka H, Hirai T, Ohki T, Ikegami M, Sawada R, Shinoda Y, Akiyama T, Sato K, Abe S, Kawano H, Goto T, Tanaka S: Neutrophil-to-lymphocyte ratio after pazopanib treatment predicts response in patients with advanced soft-tissue sarcoma. Int J Clin Oncol 2018, 23(2):368-374
29. Hosoi I, Kobayashi E, Chang SH, Matsumoto T, An Q, Anzai E, Ohta Y, Sakuma I: Development of intraoperative planter pressure measuring system considering weight bearing axis. Int J Comput Assist Radiol Surg 2018
30. Hosoi I, Kobayashi E, Chang SH, Matsumoto T, An Q, Anzai E, Ohta Y, Sakuma I: Development of intraoperative plantar pressure measuring system considering weight bearing axis. Int J Comput Assist Radiol Surg. 2018 Epub
31. Taii T, Matsumoto T, Tanaka S, Nakamura I, Ito K, Juji T: Wrist Arthrodesis in Rheumatoid Arthritis Using an LCP Metaphyseal Locking Plate versus an AO Wrist Fusion Plate. Int J Rheumatol 2018, Jul 10
32. 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: Target setting for lower limb joint surgery using the Timed Up and Go test in patients with rheumatoid arthritis: A prospective cohort study. Int J Rheum Dis 2018,21:1801-1808
33. 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 reliability of the Timed

Up and Go test for measuring objective functional impairment in patients with long-standing rheumatoid arthritis: a cross-sectional study. Int J Rheum Dis 2018, 21:1793-1800

34. Tanaka T, Moro T, Takatori Y, Oshima H, Ito H, Sugita N, Mitsuishi M, Tanaka S: Evaluation of the three-dimensional bony coverage before and after rotational acetabular osteotomy. Int Orthop 2018, 42(11):2527-2534
35. Kyomoto M, Shoyama Y, Saiga K, Moro T, Ishihara K: Reducing fretting-initiated crevice corrosion in hip simulator tests using a zirconia-toughened alumina femoral head. J Biomed Mater Res B Appl Biomater 2018, Nov 106(8)
36. Yamane S, Kyomoto M, Moro T, Hashimoto M, Takatori Y, Tanaka S, Ishihara K: Wear resistance of poly(2-methacryloyloxyethyl phosphorylcholine) -grafted carbon fiber reinforced poly(ether ether ketone) liners against metal and ceramic femoral heads. J Biomed Mater Res B Appl Biomater 2018, 106(3):1028-1037
37. Kodama R, Muraki S, Iidaka T, Oka H, Teraguchi M, Kagotani R, Asai Y, Hashizume H, Yoshida M, Kawaguchi H, Nakamura K, Akune T, Tanaka S, and Yoshimura N: Serum levels of matrix metalloproteinase-3 and autoantibodies related to rheumatoid arthritis in the general Japanese population and their association with Osteoporosis and Osteoarthritis: The ROAD Study 2018,36:246-253
38. Miura T, Ando M, Tanaka S, Uehara K: Assessment of Dorsal Subluxation in Thumb Carpometacarpal Osteoarthritis. J Hand Microsurg 2018,10:125-129
39. Inui H, Taketomi S, Yamagami R, Shirakawa N, Kawaguchi K, Tanaka S: The Relationship between Soft-Tissue Balance and Intraoperative Kinematics of Guided Motion Total Knee Arthroplasty. J Knee Surg 2018,32:91-96
40. Taketomi S, Inui H, Yamagami R, Shirakawa N, Kawaguchi K, Nakagawa T, Tanaka S: Bone-Patellar Tendon-Bone Autograft versus Hamstring Tendon Autograft for Anatomical Anterior Cruciate Ligament Reconstruction with Three-Dimensional Validation of Femoral and Tibial Tunnel Positions. J Knee Surg 2018,31: 866-874
41. Kyomoto M, Moro T, Yamane S, Watanabe K, Hashimoto M, Tanaka S, Ishihara K: A phospholipid polymer graft layer affords high resistance for wear and oxidation under load bearing conditions. J Mechan Behav Biomed Mater 2018,79:203-212
42. Hirose J, Takedani H, Nojima M, Koibuchi T: Risk factors for postoperative complications of orthopedic surgery in patients with hemophilia: Second report. J Orthop 2018, 15(2):558-562
43. Fukushima M, Oshima Y, Oka H, Chang C, Matsubayashi Y, Taniguchi Y, Matsudaira K, Tanaka S: Potential pathological mechanisms of L3 degenerative spondylolisthesis in lumbar spinal stenosis patients: A case-control study. J Orthop Sci 2018, Dec 27
44. Nagata K, Ando T, Nakamoto H, Kato S, Sasaki K, Oshima Y: Adaptation and limitation of anterior column reconstruction for pyogenic spondylitis in lower thoracic and lumbar spine. J Orthop Sci 2018, Epub
45. Taketomi S, Inui H, Yamagami R, Kawaguchi K, Nakazato K, Kono K, Kawata M, Nakagawa T, Tanaka S: Surgical timing of anterior cruciate ligament reconstruction to prevent associated meniscal and cartilage lesions. J Orthop Sci 2018, 23:546-551
46. Tanaka S: Emerging anti-osteoclast therapy for rheumatoid arthritis. J Orthop Sci 2018, 23:717-721
47. Makii Y, Asaka M, Setogawa S, Fujiki S, Hosaka Y, Yano F, Oka H, Tanaka S, Fukui N, Yanagihara D, Saito T: Alteration of gait parameters in a mouse model of surgically induced knee osteoarthritis. J Orthop Surg (Hong Kong) 2018, May-Aug;26(2)
48. Inanami H, Saiki F, Oshima Y: Microendoscope-assisted posterior lumbar interbody fusion: a technical note. Journal of Spine Surgery 2018,4: 408-413
49. Inomata Y, Oshima Y, Inoue H, Takano Y, Inanami H, Koga H: Percutaneous endoscopic lumbar discectomy via adjacent interlaminar space for highly down-migrated lumbar disc herniation: a technical report. Journal of Spine Surgery 2018, 4: 483-489
50. Ishibashi K, Oshima Y, Inoue H, Takano Y, Iwai H,

Inanami H, Koga H: A less invasive surgery using a full-endoscopic system for L5 nerve root compression caused by lumbar foraminal stenosis. Journal of Spine Surgery 2018,4:594–601

51. Kaneko T, Oshima Y, Inoue H, Iwai H, Takano Y, Inanami H, Koga H: Successful treatment of lumbar ligamentum flavum hematoma using a spinal full-endoscopic system. Journal of Spine Surgery 2018,4
52. Tonosu J, Oka H, Watanabe K, Abe H, Higashikawa A, Yamada K, Kuniya T, Nakajima K, Tanaka Matsudaira K: Validation study of a diagnostic scoring system for sacroiliac joint-related pain. J Pain Res 2018,11:1659-1663
53. Kondo M, Oshima Y, Inoue H, Takano Y, Inanami H, Koga H: Significance and pitfalls of percutaneous endoscopic lumbar discectomy for large central lumbar disc herniation. J Spine Surg 2018,4:79-85
54. Inui H, Taketomi S, Yamagami R, Kawaguchi K, Nakazato K, Tanaka S: The relationship between anteroposterior stability and medial-lateral stability of the bi-cruciate stabilized total knee arthroplasty. Knee 2018,25:1247-1253
55. Kawaguchi K, Inui H, Taketomi S, Yamagami R, Nakazato K, Shirakawa N, Tanaka S: Intraoperative mobile-bearing movement in Oxford unicompartmental knee arthroplasty. Knee Surg Sports Traumatol Arthrosc 2018, Jul 21
56. Kawata M, Sasabuchi Y, Taketomi S, Inui H, Matsui H, Fushimi K, Yasunaga H, Tanaka S: Atopic dermatitis is a novel demographic risk factor for surgical site infection after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc 2018,26:3699-3705
57. Taniguchi Y, Oichi T, Ohya J, Chikuda H, Oshima Y, Matsubayashi Y, Matsui H, Fushimi K, Tanaka S, Yasunaga H: In-hospital mortality and morbidity of pediatric scoliosis surgery in Japan: Analysis using a national inpatient database. Medicine (Baltimore) 2018, 97(14):e0277
58. Fujimoto Y, Fujii T, Oshima Y, Oka H, Tanaka S, Matsudaira K: The association between neck and shoulder discomfort-Katakori-and high somatizing tendency. Mod Rheumatol 2018, Nov 28:1-14
59. Izawa N, Hirose J, Fujii T, Oka H, Uehara K, Naito M, Matsumoto T, Tanaka S, Tohma S: The utility of 25-question Geriatric Locomotive Function Scale for evaluating functional ability and disease activity in Japanese rheumatoid arthritis patients: A cross-sectional study using NinJa database. Mod Rheumatol 2018, Apr 18:1-7
60. Matsumoto T, Maenohara Y, Chang SH, Hirose J, Juji T, Ito K, Tanaka S: Lateral collapse of the tarsal navicular in patients with rheumatoid arthritis: Implications for pes planovarus deformity. Mod Rheumatol 2018, 28(5):800-807
61. Oka H, Kadono Y, Ohashi S, Yasui T, Ono K, Matsudaira K, Nishino J, Tanaka S: Assessing joint destruction in the knees of patients with rheumatoid arthritis by using a semi-automated software for magnetic resonance imaging: therapeutic effect of methotrexate plus etanercept compared with methotrexate monotherapy. Mod Rheumatol 2018,28:235-241
62. Oka H, Nomura T, Asada F, Takano K, Nitta Y, Uchima Y, Sato T, Kawase M, Sawada S, Sakamoto K, Yasue M, Arima S, Katsuhira J, Kawamata K, Fujii T, Tanaka S, Konishi H, Okazaki H, Miyoshi K, Watanabe J, Matsudaira K: The effect of the "One Stretch" exercise on the improvement of low back pain in Japanese nurses: a large-scale, randomized, controlled trial. Mod Rheumatol 2018, Aug 22:1-17
63. Tanaka S, Tanaka Y, Ishiguro N, Yamanaka H, Takeuchi T: RANKL: A therapeutic target for bone destruction in rheumatoid arthritis. Mod Rheumatol 2018,28:9-16
64. Ogura K, Hosoda F, Arai Y, Nakamura H, Hama N, Totoki Y, Yoshida A, Nagai M, Kato M, Arakawa E, Mukai W, Rokutan H, Kawai A, Tanaka S, Shibata T: Integrated genetic and epigenetic analysis of myxofibrosarcoma. Nat Commun 2018, Jul 17;9(1):2765
65. Lucas S, Omata Y, Hofmann J, Bottcher M, Iljazovic A, Sarter K, Albrecht O, Schulz O, Krishnacoumar B, Kronke G, Herrmann M, Mougiakakos D, Strowig T, Schett G, Zaiss MM: Short-chain fatty acids regulate systemic bone mass and protect from pathological bone loss. Nat Commun 2018,9:55
66. Inoue M, Okamoto K, Terashima A, Nitta T, Muro R, Negishi-Koga T, Kitamura T, Nakashima T,

Takayanagi H: Arginine methylation controls the strength of γc-family cytokine signaling in T cell maintenance. Nature Immunology 2018,19:1265-1276

67. Yoshimura N, Muraki S, Oka H, Iidaka T, Kodama R, Horii C, Kawaguchi H, Nakamura K, Akune T, Tanaka S: Do sarcopenia and/or osteoporosis increase the risk of frailty? A 4-year observation of the second and third ROAD study surveys. Osteporos International 2018
68. Fujii T, Oka H, Katsuhira J, Tonosu J, Kasahara S, Tanaka S, Matsudaira K: Association between somatic symptom burden and health-related quality of life in people with chronic low back pain. PLoS One 2018, Feb 20;13(2):e0193208
69. Kawata M, Sasabuchi Y, Taketomi S, Inui H, Matsui H, Fushimi K, Chikuda H, Yasunaga H, Tanaka S: Annual trends in arthroscopic meniscus surgery: Analysis of a national database in Japan. PLoS One 2018:Apr 3;13(4):e0194854
70. Maeda T, Hashizume H, Yoshimura N, Oka H, Ishimoto Y, Nagata K, Takami M, Tsutsui S, Iwasaki H, Minamide A, Nakagawa Y, Yukawa Y, Muraki S, Tanaka S, Yamada H, Yoshida M: Factors associated with lumbar spinal stenosis in a large-scale, population-based cohort: The Wakayama Spine Study. PLoS One 2018,Jul 18; 13(7):e0200208
71. Ogihara S, Yamazaki T, Inanami H, Oka H, Maruyama T, Miyoshi K, Takano Y, Chikuda H, Azuma S, Kawamura N, Yamakawa K, Hara N, Oshima Y, Morii J, Okazaki R, Takeshita Y, Tanaka S, Saita K: Risk factors for surgical site infection after lumbar laminectomy and/or discectomy for degenerative diseases in adults: A prospective multicenter surveillance study with registry of 4027 cases. PLoS One 2018, Oct 16; 13(10):e0205539
72. Sasaki T, Yoshimura N, Hashizume H, Yamada H, Oka H, Matsudaira K, Iwahashi H, Shinto K, Ishimoto Y, Nagata K, Teraguchi M, Kagotani R, Muraki S, Akune T, Tanaka S, Kawaguchi H, Nakamura K, Minamide A, Nakagawa Y, Yoshida M: MRI-defined paraspinal muscle morphology in Japanese population: The Wakayama Spine Study. PLoS One 2018,12: e0187765
73. Murahashi Y, Yano F, Kobayashi H, Makii Y, Iba K, Yamashita T, Tanaka S, Saito T: Intra-articular administration of I ホコ B ホア kinase inhibitor suppresses mouse knee osteoarthritis via downregulation of the NF-kB/HIF-2α axis. Sci Rep 2018,8:16475
74. Oshina M, Oshima Y, Tanaka S, Tan LA, Li XJ, Tuchman A, Riew KD: Utility of Oblique Sagittal Reformatted and Three-dimensional Surface Reconstruction Computed Tomography in Foraminal Stenosis Decompression. Sci Rep 2018, 8(1):16011
75. Yamada K, Abe H, Higashikawa A, Tonosu J, Kuniya T, Nakajima K, Fujii H, Niwa K, Shinozaki T, Watanabe K, Sakae T, Okazaki H: Evidence-based Care Bundles for Preventing Surgical Site Infections in Spinal Instrumentation Surgery. Spine (Phila Pa 1976) 2018, 43:1765-1773
76. Anno M, Oshima Y, Taniguchi Y, Matsubayashi Y, Kato S, Soma K, Oka H, Hayashi N, Tanaka S: Prevalence and Natural Course of Transverse Ligament of the Atlas Calcification in Asymptomatic Healthy Individuals. Spine (Phila Pa 1976) 2018,43(24):E1469-E1473
77. Kato S, Fehlings MG, Lewis SJ, Lenke LG, Shaffrey CI, Cheung KMC, Carreon LY, Dekutoski MB, Schwab FJ, Boachie-Adjei O, Kebaish KM, Ames CP, Qiu Y, Matsuyama Y, Dahl BT, Mehdian H, Pellis F, Berven SH: An Analysis of the Incidence and Outcomes of Major Versus Minor Neurological Decline After Complex Adult Spinal Deformity Surgery: A Subanalysis of Scoli-RISK-1 Study. Spine (Phila Pa 1977) 2018, 43(13):905-912
78. Kato S, Fok KL, Lee JW, Masani K: Dynamic Fluctuation of Truncal Shift Parameters During Quiet Standing in Healthy Young Individuals. Spine (Phila Pa 1978) 2018, 43(13):E746-E751
79. Kato S, Nouri A, Reihani-Kermani H, Oshima Y, Cheng J, Fehlings MG: Postoperative Resolution of Magnetic Resonance Imaging Signal Intensity Changes and the Associated Impact on Outcomes in Degenerative Cervical Myelopathy: Analysis of a Global Cohort of Patients. Spine (Phila Pa 1979) 2018, 43(12):824-831
80. Kato S, Nouri A, Wu D, Nori S, Tetreault L, Fehlings MG: Impact of Cervical Spine

Deformity on Preoperative Disease Severity and Postoperative Outcomes Following Fusion Surgery for Degenerative Cervical Myelopathy: Sub-analysis of AOSpine North America and International Studies. Spine (Phila Pa 1980) 2018, 43(4):248-254

81. Kato S, Oshima Y, Matsubayashi Y, Taniguchi Y, Tanaka S, Takeshita K: Minimum Clinically Important Difference and Patient Acceptable Symptom State of Japanese Orthopaedic Association Score in Degenerative Cervical Myelopathy Patients. Spine (Phila Pa 1981) 2018, Epub
82. Oichi T, Oshima Y, Matsui H, Fushimi K, Tanaka S, Yasunaga H: Can Elective Spine Surgery be Performed Safely Among Nonagenarians? Analysis of a National Inpatient Database in Japan. Spine (Phila Pa 1982) 2018, Epub
83. Oichi T, Taniguchi Y, Soma K, Chang SH, Yano F, Tanaka S, Saito T: A Mouse Intervertebral Disc Degeneration Model by Surgically Induced Instability. Spine (Phila Pa 1983) 2018, 43(10): E557-E564
84. Fehlings MG, Kato S, Lenke LG, Nakashima H, Nagoshi N, Shaffrey CI, Cheung KMC, Carreon L, Dekutoski MB, Schwab FJ, Boachie-Adjei O, Kebaish KM, Ames CP, Qiu Y, Matsuyama Y, Dahl BT, Mehdian H, Pellise-Urquiza F, Lewis SJ, Berven SH: Incidence and risk factors of postoperative neurologic decline after complex adult spinal deformity surgery: results of the Scoli-RISK-1 study. Spine J 2018, 18(10):1733-1740
85. Horii C, Yamazaki T, Oka H, Azuma S, Ogihara S, Okazaki R, Kawamura N, Takano Y, Morii J, Takeshita Y, Maruyama T, Yamakawa K, Murakami M, Oshima Y, Tanaka S: Does intrawound vancomycin powder reduce surgical site infection after posterior instrumented spinal surgery? A propensity score-matched. Spine J 2018, 18(12):2205-2212
86. Kato S, Hozumi T, Yamakawa K, Saiki H, Sugita S, Oshima Y, Tanaka S: Letter to the Editor concerning "The META score for differentiating metastatic from osteoporotic vertebral fractures: an independent agreement assessment" by Besa etal.. Spine J 2018,18(11):2167-2168
87. Oichi T, Oshima Y, Chikuda H, Ohya J, Matsui H, Fushimi K, Tanaka S, Yasunaga H: In-hospital complication rate following microendoscopic versus open lumbar laminectomy: a propensity score-matched analysis. Spine J 2018, 18(10)
88. Emoto S, Kaneko M, Murono K, Sasaki K, Otani K, Nishikawa T, Tanaka T, Hata K, Kawai K, Imai H, Saito N, Kobayashi H, Tanaka S, Ikemura M, Ushiku T, Nozawa H: Surgical management for a huge presacral teratoma and a meningocele in an adult with Currarino triad: a case report. Surg Case Rep 2018, Jan 19;4(1):9
89. Uehara K, Zhao C, Amadio PC: Fibrin glue as an alternative to peripheral sutures does not increase tendon repair strength in an in vitro model. J Hand Surg Eur Vol 2018,43:995-997
90. 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 2018, Nov 13. pii:S0949-2658(18)30317-8
91. Izawa N, Hirose J, Fujii T, Oka H, Uehara K, Naito M, Matsumoto T, Tanaka S, Tohma S: The utility of 25-question Geriatric Locomotive Function Scale for evaluating functional ability and disease activity in Japanese rheumatoid arthritis patients: A cross-sectional study using NinJa database. Mod Rheumatol 2018,18
92. Saita K, Monobe Y, Ogihara S, Kobayashi Y, Sato K, Nishimura K, Tanabe M: A case of vertebral fracture associated with diffuse idiopathic skeletal hyperostosis treated by successful conservative treatment. Spine Surgery and Related Research 2018, Epub

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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. Aihara M, Kubota N, Minami T, Shirakawa R, Sakurai Y, Hayashi T, Iwamoto M, Takamoto I, Kubota T, Suzuki R, Usami S, Jinnouchi H, Aihara M, Yamauchi T, Sakata T, Kadowaki T. Association between tear and blood glucose concentrations: Random intercept model
2. Azuma K, Okubo A, Suzuki T, Igarashi N, Nomura Y, Soga H, Murata H, Fujino R, Ogawa A, Matsui H, Nagamatsu T, Iriyama T, Asaoka R, Inoue T, Maruyama-Inoue M, Kadonosono K, Obata R. Assessment of the choroidal structure in pregnant women in the first trimester. Sci Rep. 2021 Feb 25;11(1):4629.
3. Igarashi N, Honjo M, Asaoka R, Kurano M, Yatomi Y, Igarashi K, Miyata K, Kaburaki T, Aihara M. Aqueous autotaxin and TGF-βs are promising diagnostic biomarkers for distinguishing open-angle glaucoma subtypes. Sci Rep. 2021 Jan 14;11(1):1408.
4. Obata R, Yoshinaga A, Yamamoto M, Komatsu K, Aoki N, Yamanari M, Sugiyama S, Minami T, Azuma K, Inoue T, Aihara M, Kato S. Obata R, Yoshinaga A, Yamamoto M, Komatsu K, Aoki N, Yamanari M, Sugiyama S, Minami T, Azuma K, Inoue T, Aihara M, Kato S. Jpn J Ophthalmol. 2021 Jan;65(1):30-41.
5. Omoto T, Sugiura A, Fujishiro T, Asano-Shimizu K, Sugimoto K, Sakata R, Murata H, Asaoka R, Honjo M, Aihara M. Twelve-month surgical outcome and prognostic factors of stand-alone ab interno trabeculotomy in Japanese patients with open-angle glaucoma. PLoS One. 2021 Jan 7; 16(1):e0245015.
6. Honjo M, Yamagishi R, Igarashi N, Ku CY, Kurano M, Yatomi Y, Igarashi K, Aihara M. Effect of postoperative corticosteroids on surgical outcome and aqueous autotaxin following combined cataract and microhook ab interno trabeculotomy. Sci Rep. 2021 Jan 12; 11(1):747.
7. Hashimoto Y, Michihata N, Yamana H, Shigemi D, Morita K, Matsui H, Yasunaga H, Aihara M. Intraocular pressure-lowering medications during pregnancy and risk of neonatal adverse outcomes: a propensity score analysis using a

large database. Br J Ophthalmol. 2021 Oct; 105(10):1390-1394.

8. Nakamura N, Honjo M, Yamagishi R, Kurano M, Yatomi Y, Watanabe S, Aihara M. Neuroprotective role of sphingolipid rheostat in excitotoxic retinal ganglion cell death. Exp Eye Res. 2021 Jul;208:108623.
9. Fujita A, Amari T, Ueda K, Azuma K, Inoue T, Komatsu K, Yamamoto M, Aoki N, Yamanari M, Sugiyama S, Aihara M, Kato S, Obata R. Three-Dimensional Distribution Of Fundus Depolarization and Associating Factors Measured Using Polarization-Sensitive Optical Coherence Tomography. Transl Vis Sci Technol. 2021 Feb 5;10(2):30.
10. Kitano M, Fujita A, Asaoka R, Inoue T, Amari T, Komatsu K, Yamamoto M, Ogawa A, Aoki N, Yamanari M, Sugiyama S, Aihara M, Kato S, Azuma K, Maruyama-Inoue M, Kadonosono K, Obata R. Assessment of macular function in patients with non-vascularized pigment epithelial detachment. Sci Rep. 2021 Aug 16;11(1):16577.
11. Shirahama S, Soga H, Tanaka R, Fukunaga H, Izawa H, Komae K, Nakahara H, Kawashima H, Aihara M, Kaburaki T. Clinical features of uveitis in elderly patients in central Tokyo (2013-2018). Int Ophthalmol. 2021 May;41(5): 1671-1679.
12. Sakata R, Fujishiro T, Saito H, Honjo M, Shirato S, Aihara M. The Additive Effect of ROCK Inhibitor on Prostaglandin-Treated Japanese Patients with Glaucoma Indicating 15 mmHg and Under: ROCK U-15. Adv Ther. 2021 Jul;38(7): 3760-3770.
13. Nakamura N, Honjo M, Yamagishi R, Igarashi N, Sakata R, Aihara M. Effects of selective EP2 receptor agonist, omidenepag, on trabecular meshwork cells, Schlemm's canal endothelial cells and ciliary muscle contraction. Sci Rep. 2021 Aug 10;11(1):16257.
14. Zhou HP, Ishikawa H, Yasumoto R, Sakurai K, Sawamura H. Leber hereditary optic neuropathy harboring a rare m.12811 T>C mitochondrial DNA mutation. Canadian Journal of Ophthalmology. 2021; 56: 82-84.
15. Terao R, Matsuda A, Ogawa A, Shimizu K, Azuma K, Inoue T, Obata R. OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY STUDY OF CHOROIDAL NEOVASCULARIZATION ASSOCIATED WITH EARLY-ONSET DRUSEN. Retin Cases Brief Rep. 2021 Sep 1;15(5):581-587.
16. M, Ueta T. Fovea-Sparing as Opposed to Total Peeling of Internal Limiting Membrane for Myopic Foveoschisis: A Systematic Review and Meta-analysis. Ophthalmol Retina. 2021; 5: 670-679.
17. 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; 11: 18224.
18. Tanaka R, Kaburaki T, Taoka K, Karakawa A, Tsuji H, Nishikawa M, Yatomi Y, Shinozaki-Ushiku A, Ushiku T, Araki F. More Accurate Diagnosis of Vitreoretinal Lymphoma Using a Combination of Diagnostic Test Results: A Prospective Observational Study. Ocul Immunol Inflamm. 2021; 1-7.
19. Takao-Okuma H, Terao R, Nagahara M, Azuma K, Inoue T, Uemura Y, Obata R. Distribution of recurrence time intervals after anti-vascular endothelial growth factor therapy for myopic choroidal neovascularization. Can J Ophthalmol. 2021 Apr; 56(2): 137-138.
20. Agata C, Kitamoto K, Ueda K, Azuma K, Inoue T, Obata R. Rapidly Changing Serous Detachment During BRAF and MEK Inhibitor Therapy. Cureus. 2021 Dec 17;13(12):e20491.
21. Kanda S, Fujishiro T, Omoto T, Fujino R, Ishii K, Aihara M. The effects of antithrombotic therapy in ab interno trabeculotomy with a spatula-shaped microhook. PLoS One. 2022 Jan 13; 17(1): e0262548.
22. Soga H, Asaoka R, Kadonosono K, Maruyama-Inoue M, Igarashi N, Kitano M, Kitamoto K, Azuma K, Obata R, Inoue T. Association of Near-Infrared and Short-Wavelength Auto-fluorescence With the Retinal Sensitivity in Eyes With Resolved Central Serous Chorioretinopathy. Invest Ophthalmol Vis Sci. 2021 Mar 1;62(3):36.

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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 otorhino-laryngological 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 paresis, vertigo and balance disorders, olfactory disorders and paranasal diseases, voice and speech disorders, taste and swallowing respiratory disorders, aphasia, central auditory disorders and head & neck cancers.

A professor, associate professors, lecturers (assistant professors) and associates participate in surgery, out-patient and in-patient care as well as research and educational activities. Moreover 8 Japanese graduate students and two Chinese foreign 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 on a regular basis. A weekly 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 new inpatient hospital, 33 beds are prepared for patients under the supervision of lecturers and senior residents 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 700 operations are performed annually.

Cochlear implant surgery over 400 cases has been actively 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.

Treatment of acoustic tumor using an γ-knife and auditory brainstem implant are performed in consultation with neurosurgeons.

Teaching activities

For the fourth year medical students' serial lectures and for the fifth and sixth year medical students special lectures on current topics are provided by the professor and associate professor.

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. Interview with patient is encouraged. They are questioned on many aspects of clinical problems in seminars by professor and associate professor.

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, broncho-esophagology 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) Speech perception and language development in deaf children
3) Liquid biopsy of perilymph via round window membrane
4) Prediction of hearing outcome in tympanoplasty using machine learning
5) Analysis of balance disorders using vestibular function tests
6) Development of novel examination methods for balance disorders
7) Development of novel therapeutic methods for balance disorders by galvanic vestibular stimulation
8) Predicting and elucidating the pathogenesis of vestibular disorders using machine learning
9) Elucidation of the pathogenesis of vestibular migraine
10) Development of novel therapeutic methods for persistent postural-perceptual dizziness
11) Elucidation of the mechanism of postural control in patients with vestibulopathy using mathematical models
12) Hair cell physiology and pathology and

introduction of hair cell regeneration in the auditory and vestibular end organ
13) Clinical neurophysiology of the facial nerves focusing on degeneration and regeneration in patients
14) Analyses of development, regeneration and aging in olfactory neural system
15) Pathophysiology of olfactory dysfunction
16) Computer fluid dynamics of intranasal airflow
17) Metabolic conversion of odorant molecules by nasal mucus
18) Analysis of eosinophilic chronic sinusitis using human samples and animal models
19) Pulmonary inflammatory responses by contrast agent aspiration
20) Swallowing mechanisms using pathological and electrophysiological analysis and VR system
21) Evaluation of swallowing physiology with pharyngo-esophageal high-resolution manometry
22) Esophageal Motility in Neuromuscular Disorders
23) Gene expression analysis of recurrent respiratory papillomatosis
24) Kinetics of vocal cord movement using high-speed video system
25) Histochemical, molecular biological, and genome analysis of head and neck cancer

Various clinical and basic research is conducted by staffs, residents, and graduate students as well as doctors at affiliated hospitals.

References

1. Asakura S, Kamogashira T. Sudden bilateral hearing loss after vestibular-evoked myogenic potentials. Clin Case Rep. 9(11):e05025. 2021
2. Baba S, Kondo K, Yoshitomi A, Kanemaru A, Nakaya M, Yamasoba T. Efficacy of Mirror Biofeedback Rehabilitation on Synkinesis in Acute Stage Facial Palsy in Children. Otol Neurotol. 42(7):e936-e41. 2021
3. Eguchi K, Kobayashi K, Takano T, Ito A, Sakai A, Ikeda A, Matsumoto Y, Omura G, Matsumoto F, Yoshimoto S. Carotid artery ligation via sternotomy as a palliative surgery: Case report of advanced intramediastinal malignant soft tissue tumor. Clin Case Rep. 9(8). 2021
4. Fujimoto C, Kawahara T, Kinoshita M, Ichijo K, Oka M, Kamogashira T, Sugasawa K, Yamasoba T, Iwasaki S. Minimally important differences for subjective improvement in postural stability in patients with bilateral vestibulopathy. Neurosci Lett. 747. 135706, 2021
5. Fujimoto C, Kinoshita M, Ichijo K, Oka M, Kamogashira T, Sugasawa K, Kawahara T, Yamasoba T, Iwasaki S. Cervical Vestibular Evoked Myogenic Potentials That Are Absent at 500 Hz But Present at 1000 Hz Are Characteristic of Endolymphatic Hydrops-Related Disease. Ear Hearing. 42(5):1306-12. 2021
6. Fujisawa K, Miyamoto S, Saito Y, Fukuoka O, Okazaki M. Total Maxillectomy and Free Flap Reconstruction in Hemodialysis Patients: Report of Two Cases. Prs-Glob Open. 9(11). 2021
7. Fukusumi T, Guo TW, Ren SL, Haft S, Liu C, Sakai A, Ando M, Saito Y, Sadat S, Califano JA. Reciprocal activation of HEY1 and NOTCH4 under SOX2 control promotes EMT in head and neck squamous cell carcinoma. Int J Oncol. 58(2): 226-37. 2021
8. Igarashi K, Cabral H, Hong TH, Anraku Y, Mpekris F, Stylianopoulos T, Khan T, Matsumoto A, Kataoka K, Matsumoto Y, Yamasoba T. Vascular Bursts Act as a Versatile Tumor Vessel Permeation Route for Blood-Borne Particles and Cells. Small. 17(42). 2021
9. Ijichi C, Wakabayashi H, Sugiyama S, Hayashi K, Ihara Y, Nishijima H, Touhara K, Kondo K. Odorant metabolism of the olfactory cleft mucus in idiopathic olfactory impairment patients and healthy volunteers. Int Forum Allergy Rhinol. 10.1002/alr.22897, 2021
10. Imoto Y, Sakashita M, Hayama M, Nakamaru Y, Suzuki M, Miyabe Y, Yamada T, Saito H, Yonekura S, Kondo K, Higaki T, Kawashima K, Urashima M, Fujieda S. The clinical features of intractable allergic rhinitis based on a questionnaire administered to clinicians. Allergology international: official journal of the Japanese Society of Allergology. 70(3):373-5. 2021
11. Inoue Y, Matsumoto Y, Toh K, Miyano K, Cabral H, Igarashi K, Iwasaki S, Kataoka K, Yamasoba T. Manipulating dynamic tumor vessel permeability

to enhance polymeric micelle accumulation. J Control Release. 329:63-75. 2021
12. Iritani O, Okuno T, Miwa T, Makizako H, Okutani F, Kashibayashi T, Suzuki K, Hara H, Mori E, Omoto S, Suzuki H, Shibata M, Adachi H, Kondo K, Umeda-Kameyama Y, Kodera K, Morimoto S. Olfactory-cognitive index distinguishes involvement of frontal lobe shrinkage, as in sarcopenia from shrinkage of medial temporal areas, and global brain, as in Kihon Checklist frailty/ dependence, in older adults with progression of normal cognition to Alzheimer's disease. Geriatr Gerontol Int. 21(3):291-8. 2021
13. Ito A, Kobayashi K, Shiotsuka M, Sato T, Omura G, Matsumoto Y, Ikeda A, Sakai A, Eguchi K, Takano T, Matsumoto F, Kobayashi O, Iwata S, Yoshimoto S. Uniform infection screening allowed safe head and neck surgery during the coronavirus disease 2019 pandemic in Japan. Jpn J Clin Oncol. 51(3):400-7. 2021
14. Ito Y, Nishijima H, Kishimoto S. A Case of Huge Cutaneous Verrucous Carcinoma of the Neck. Cureus. 13(5). 2021
15. Iwaki H, Kamiya M, Kawatani M, Kojima R, Yamasoba T, Urano Y. Fluorescence Probes for Imaging Basic Carboxypeptidase Activity in Living Cells with High Intracellular Retention. Anal Chem. 93(7):3470-6. 2021
16. Kagoya R, Kondo K, Kishimoto-Urata M, Shimizu Y, Kikuta S, Yamasoba T. A murine model of eosinophilic chronic rhinosinusitis using the topical application of a vitamin D3 analog. Allergy. 76(5):1432-42. 2021
17. Kashihara T, Nakamura S, Murakami N, Ito K, Matsumoto Y, Kobayashi K, Omura G, Mori T, Honma Y, Kubo Y, Okamoto H, Takahashi K, Inaba K, Okuma K, Igaki H, Nakayama Y, Kato K, Matsumoto F, Yoshimoto S, Itami J. Initial Experience of Intentional Internal High-Dose Policy Volumetric Modulated Arc Therapy of Neck Lymph Node Metastases >= 2 cm in Patients With Head and Neck Squamous Cell Carcinoma. Front Oncol. 11. 2021
18. Kashio A, Takahashi H, Nishizaki K, Hara A, Yamasoba T, Moriyama H. Cochlear implants in Japan: Results of cochlear implant reporting system over more than 30 years. Auris Nasus Larynx. 48(4):622-9. 2021
19. Katano A, Takenaka R, Yamashita H, Ando M, Yoshida M, Saito Y, Asakage T, Abe O, Nakagawa K. A retrospective analysis of radiotherapy in the treatment of external auditory canal carcinoma. Mol Clin Oncol. 14(3). 2021
20. Kataoka T, Yoshida S, Ueha R. Clicking Sensation on Swallowing. Jama Otolaryngol. 147(8):762-3. 2021
21. Kikuta S, Kuboki A, Yamasoba T. Protective Effect of Insulin in Mouse Nasal Mucus Against Olfactory Epithelium Injury. Front Neural Circuits. 15:803769. 2021
22. Kobayashi K, Yoshimoto S, Ando M, Matsumoto F, Murakami N, Omura G, Honma Y, Matsumoto Y, Ikeda A, Sakai A, Eguchi K, Ito A, Ryo E, Yatabe Y, Mori T. Full-coverage TP53 deep sequencing of recurrent head and neck squamous cell carcinoma facilitates prognostic assessment after recurrence. Oral Oncol. 113. 2021
23. Kobayashi K, Miyatkita Y, Matsumoto F, Omura G, Matsumura S, Ikeda A, Eguchi K, Ito A, Narita Y, Akazawa S, Yoshimoto S. Olfactory Preservation in Craniofacial Resection of Tumor Invading Hemianterior Skull Base: Operative Video. J Neurol Surg B Skull Base. doi: 10.1055/s-0041-1727123. 2021
24. Kobayashi T, Iwamoto S, Shiraishi K, Mori A, Koyama H, Fujita T, Osaki Y, Doi K. Evaluation of Vestibular Disorder Risk Associated with Middle Ear Surgery Clinics in Surgery. 1:3063. 2021
25. Koizumi M, Ishimaru M, Matsui H, Fushimi K, Yamasoba T, Yasunaga H. Factors associated with the occurrence of stomal stenosis after tracheostomy in adults. Auris Nasus Larynx. 48(5):973-7. 2021
26. Koyama H, Kashio A, Fujimoto C, Uranaka T, Matsumoto Y, Kamogashira T, Kinoshita M, Iwasaki S, Yamasoba T. Alteration of Vestibular Function in Pediatric Cochlear Implant Recipients. Front Neurol. 12:661302. 2021
27. Koyama H, Mori A, Nagatomi D, Fujita T, Saito K, Osaki Y, Yamasoba T, Doi K. Machine Learning Technique Reveals Prognostic Factors of Vibrant Soundbridge for Conductive or Mixed

Hearing Loss Patients. Otol Neurotol. 42(9): e1286-e92. 2021
28. Koyama S, Kondo K, Ueha R, Kashiwadani H, Heinbockel T. Possible Use of Phytochemicals for Recovery from COVID-19-Induced Anosmia and Ageusia. International journal of molecular sciences. 22(16). 2021
29. Koyama S, Ueha R, Kondo K. Loss of Smell and Taste in Patients With Suspected COVID-19: Analyses of Patients' Reports on Social Media. J Med Internet Res. 23(4). 2021
30. Kuboki A, Kikuta S, Otori N, Kojima H, Matsumoto I, Reisert J, Yamasoba T. Insulin-Dependent Maturation of Newly Generated Olfactory Sensory Neurons after Injury. eNeuro. 8(3):0618-21. 2021
31. Lin N, Urata S, Cook R, Makishima T. Sex differences in the auditory functions of rodents. Hearing research.108271. 2021
32. Masuda H, Ueha R, Sato T, Goto T, Koyama M, Yamauchi A, Kaneoka A, Suzuki S, Yamasoba T. Risk Factors for Aspiration Pneumonia After Receiving Liquid-Thickening Recommendations. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. doi: 10.1177/ 0194599821104911 4. 2021
33. Matsumoto F, Miyakita Y, Sakai A, Akamatsu M, Matsumoto Y, Matsumura S, Omura G, Kobayashi K, Narita Y, Yoshimoto S. Resection of carcinoma of the external auditory canal in a patient with a high jugular bulb using temporal craniotomy. Auris Nasus Larynx. 48(3):535-8. 2021
34. Meng X, Matsumoto F, Mori T, Miura N, Ino Y, Onidani K, Kobayashi K, Matsuzaki Y, Yoshimoto S, Ikeda K, Honda K. BP180 Is a Prognostic Factor in Head and Neck Squamous Cell Carcinoma. Anticancer Res. 41(2):1089-99. 2021
35. Mori A, Takeda H, Kobayashi M, Misawa T, Watanabe R, Abe S, Kumakawa K, Nishio S, Usami S, Yamasoba T. Successful cochlear implantation in a patient with Epstein syndrome during long-term follow-up. Auris Nasus Larynx doi: 10.1016/j.anl.2020.09.008. 2020
36. Mori E, Ueha R, Kondo K, Funada S, Shimmura H, Kanemoto K, Tanaka H, Nishijima H, Otori N, Yamasoba T, Kojima H. Squamous and Respiratory Metaplasia After Olfactory Mucosal Resection. Front Neurosci. 15:695653. 2021
37. Namba S, Ueno T, Kojima S, Kobayashi K, Kawase K, Tanaka Y, Inoue S, Kishigami F, Kawashima S, Maeda N, Ogawa T, Hazama S, Togashi Y, Ando M, Shiraishi Y, Mano H, Kawazu M. Transcript-targeted analysis reveals isoform alterations and double-hop fusions in breast cancer. Commun Biol. 4(1):1320. 2021
38. Nativ-Zeltzer N, Ueha R, Nachalon Y, Ma B, Pastenkos G, Swackhamer C, Bornhorst GM, Lefton-Greif MA, Anderson JD, Belafsky PC. Inflammatory Effects of Thickened Water on the Lungs in a Murine Model of Recurrent Aspiration. Laryngoscope. 131(6):1223-8. 2021
39. Ogawa K, Asano K, Yotsumoto S, Yamane T, Arita M, Hayashi Y, Harada H, Makino-Okamura C, Fukuyama H, Kondo K, Yamasoba T, Tanaka M. Frontline Science: Conversion of neutrophils into atypical Ly6G(+)SiglecF(+)immune cells with neurosupportive potential in olfactory neuroepithelium. J Leukocyte Biol. 109(3):481-96. 2021
40. Okano M, Kondo K, Takeuchi M, Taguchi Y, Fujita H. Health-related quality of life and drug treatment satisfaction were low and correlated negatively with symptoms in patients having severe refractory chronic rhinosinusitis with nasal polyps. Allergology International. 70(3):370-2. 2021
41. Okano S, Homma A, Kiyota N, Tahara M, Hanai N, Asakage T, Matsuura K, Ogawa T, Saito Y, Sano D, Kodaira T, Motegi A, Yasuda K, Takahashi S, Tanaka K, Onoe T, Yokota T, Imamura Y, Ariizumi Y, Akimoto T, Hayashi R. Induction chemotherapy in locally advanced squamous cell carcinoma of the head and neck. Jpn J Clin Oncol. 51(2):173-9. 2021
42. Omura K, Han B, Nishijima H, Aoki S, Ebihara T, Kondo K, Otori N, Kojima H, Yamasoba T, Kikuta S. Heterogeneous distribution of mature olfactory sensory neurons in human olfactory epithelium. Int Forum Allergy Rhinol. 10.1002/ alr.22885, 2021

43. Sano N, Kikuta S, Kondo K, Yamasoba T. High CT values relative to the brainstem differentiate inverted papillomas from nasal polyps. Auris Nasus Larynx. 48(5):905-13. 2021
44. Sato D, Hasegawa H, Shin M, Kondo K, Saito N. Combined endoscopic endonasal transtubercular and transclival approaches for large neurenteric cyst in posterior cranial fossa: A case report and literature review. Surg Neurol Int. 12:554. 2021
45. Sato T, Ueha R, Goto T, Yamauchi A, Kondo K, Yamasoba T. Expression of ACE2 and TMPRSS2 Proteins in the Upper and Lower Aerodigestive Tracts of Rats: Implications on COVID 19 Infections. Laryngoscope. 131(3):E932-E9. 2021
46. Sekiguchi Koyama M, Ueha R, Goto T, Sato T, Tachibana A, Mizumoto Y, Nito T, Yamasoba T. Aspiration Prevention Surgery under Local Anesthesia for Palliative Care in Patients with Head and Neck Cancer: A Report of Two Cases. ORL J Otorhinolaryngol Relat Spec. 83(1):52-8. 2021
47. Shibasaki H, Kinoh H, Cabral H, Quader S, Mochida Y, Liu X, Toh K, Miyano K, Matsumoto Y, Yamasoba T, Kataoka K. Efficacy of pH-Sensitive Nanomedicines in Tumors with Different c-MYC Expression Depends on the Intratumoral Activation Profile. ACS nano. 15(3): 5545-59. 2021
48. Shinya Y, Hasegawa H, Shin M, Sugiyama T, Kawashima M, Katano A, Kashio A, Kondo K, Saito N. Long-Term Outcomes of Stereotactic Radiosurgery for Trigeminal, Facial, and Jugular Foramen Schwannoma in Comparison with Vestibular Schwannoma. Cancers. 13(5). 2021
49. Sugaya T, Ueha R, Sato T, Goto T, Yamauchi A, Yamasoba T. Safety of surgical tracheostomy under continued antithrombotic therapy: A retrospective cohort study. Clinical otolaryngology. doi: 10.1111/coa.13861.2021
50. Suzuki T, Maruyama J, Cook R, Urata S, Paessler S, Makishima T. Auditory function analysis in immunodeficient STAT1 knock-out mice: Considerations for viral infection models. Neurosci Lett. 740:135427. 2021
51. Takabayashi T, Asaka D, Okamoto Y, Himi T, Haruna S, Yoshida N, Kondo K, Yoshikawa M, Sakuma Y, Shibata K, Suzuki M, Kobayashi M, Kawata R, Tsuzuki K, Okano M, Higaki T, Takeno S, Kodama S, Yonekura S, Saito H, Nozaki A, Otori N, Fujieda S. A Phase II, Multicenter, Randomized, Placebo-Controlled Study of Benralizumab, a Humanized Anti-IL-5R Alpha Monoclonal Antibody, in Patients With Eosinophilic Chronic Rhinosinusitis. Am J Rhinol Allergy. 35(6):861-70. 2021
52. Takamizawa S, Honma Y, Murakami N, Mori T, Oka H, Yamamoto S, Kashihara T, Ito K, Kubo Y, Ikeda A, Matsumoto F, Omura G, Kobayashi K, Itami J, Kato K, Yoshimoto S. Short-term outcomes of induction chemotherapy with docetaxel, cisplatin, and fluorouracil (TPF) in locally advanced nasopharyngeal carcinoma. Invest New Drugs. 39(2):564-70. 2021
53. Ueha R, Kondo K, Kagoya R, Shichino S, Shichino S, Yamasoba T. ACE2, TMPRSS2, and Furin expression in the nose and olfactory bulb in mice and humans. Rhinology. 59(1):105-9. 2021
54. Ueha R, Sato T, Goto T, Koyama M, Yamauchi A, Mizukami A, Yamasoba T. Effects of Aspiration Prevention Surgery on the Dynamics of the Pharynx and Upper Esophageal Sphincter. OTO Open. 5(4):2473974X211048505. 2021
55. Ueha R, Sato T, Goto T, Yamauchi A, Nativ-Zeltzer N, Mitsui J, Belafsky PC, Yamasoba T. Esophageal Dysmotility is Common in Patients With Multiple System Atrophy. Laryngoscope. 131(4):832-8. 2021
56. Uranaka T, Kashio A, Ueha R, Sato T, Bing H, Ying G, Kinoshita M, Kondo K, Yamasoba T. Expression of ACE2, TMPRSS2, and Furin in Mouse Ear Tissue, and the Implications for SARS-CoV-2 Infection. Laryngoscope. 131(6):E2013-E7. 2021
57. Uranaka T, Matsumoto Y, Hoshi Y, Iwasaki S, Kakigi A, Yamasoba T. Classification of the Chorda Tympani: An Endoscopic Study. Otol Neurotol. 42(3):e355-e62. 2021
58. Urata S, Maruyama J, Kishimoto-Urata M, Sattler RA, Cook R, Lin N, Yamasoba T, Makishima T, Paessler S. Regeneration Profiles of Olfactory Epithelium after SARS-CoV-2 Infection in Golden Syrian Hamsters. ACS Chem Neurosci. 12(4):589-95. 2021

59. Yamauchi A, Imagawa H, Yokonishi H, Sakakibara KI, Tayama N. Multivariate Analysis of Vocal Fold Vibrations on Various Voice Disorders Using High-Speed Digital Imaging. Appl Sci 11, 2021. https://doi.org/10.3390/app11146284
60. Yamauchi A, Imagawa H, Yokonishi H, Sakakibara KI, Tayama N. Multivariate analysis of vocal fold vibration in normal speakers using high-speed digital imaging. J Voice. doi: 10.1016/j. jvoice.2021.08.002. 2021
61. Yamakawa K, Kondo K, Unaki A, Saigusa H, Horikiri K, Yamasoba T. Gustatory rhinitis in multiple system atrophy. Acta Oto-Laryngol Ca. 6(1):67-70. 2021
62. Yamagishi J, Kagoya R, Saito M, Fujimoto C, Kikuchi H, Ito K. Acute pharyngitis with the abrupt manifestation of neurological disorders, leading to a diagnosis of Neuro-Behcet's disease. Acta Otolaryngol Case Rep 6:71-74. 2021
63. Yazaki S, Yoshida T, Kojima Y, Yagishita S, Nakahama H, Okinaka K, Matsushita H, Shiotsuka M, Kobayashi O, Iwata S, Narita Y, Ohba A, Takahashi M, Iwasa S, Kobayashi K, Ohe Y, Yoshida T, Hamada A, Doi T, Yamamoto N. Difference in SARS-CoV-2 Antibody Status Between Patients With Cancer and Health Care Workers During the COVID-19 Pandemic in Japan. Jama Oncol. 7(8):1141-8. 2021

Department of Rehabilitation Medicine

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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 musculo-skeletal 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. Neuro-psychopharmacol 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

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Introduction and Organization

The Department of Anesthesiology was established in 1952 and is the oldest department of anesthesiology in Japan. As of March 1, 2022, the Department of Anesthesiology consists of Professor Kanji Uchida; Associate Professor Masahiko Sumitani; Project Associate Professor Maiko Hasegawa; Lecturers Nobuko Ito, Masahiko Bougaki, Yoshiteru Mori, Gaku Kawamura, Taro Kariya, Masaaki Asamoto; 24 Associates, 14 anesthesiology residents, and 6 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. After a decrease in FY2020 due to COVID-19 pandemic, the total number of surgeries in FY2021 (Apr 2021 – Mar 2022) was 11,047, of which the anesthesiologists managed 8,289 cases. 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 1,736 preoperative patients in FY2021. We have participated in the Perioperative Management Center Program and are designing and implementing a system for more efficient and appropriate perioperative patient management. 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 1,202 (1,110 in FY2020) in FY2021.

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 FY2021 was 307 (308 in FY2020). The number of neuraxial labor analgesia was 363 (365 in FY2020) in FY2021.

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 FY2021 was 5,112 (6,090 in FY2020), of which 296 were first-time patients (215 in FY2020). The number of active beds was 1, and the number of inpatients was 15. There were 125 requests for pain consultation for inpatients in FY2021.

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 FY2021 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. In accordance with the policy of the School of Medicine in response to the outbreak of COVID-19, the Clinical Clerkship for the period from January to March 2021 was conducted online.

For post-graduate education, we accepted a total of 104 junior residents of PGY1 and 2 from the General Education Center as rotators (1-2 months for each rotator) in FY2020. The training includes anesthesia management, preoperative and intraoperative management, and basic skills and knowledge in emergency and resuscitation settings. For the 14 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.

Publications

1. Aoyama H, Uchida K. Respiratory characteristics and related intraoperative ventilatory management for patients with COVID-19 pneumonia. *J Anesth.* 2021;35:356-360.
2. Ikeda T, Orii R, Iwakiri M, Uchida K, Yamada Y. Unexpected deposits in the anesthetic circuit: A possible cause of PEEP/Pmax valve malfunction. *J Clin Monit Comput.* 2021;35:943-948.

3. Inoue R, Abe H, Konishi M, Tsuchida R, Edamura T, Sumitani M. Capecitabine induced hand foot syndrome does not emerge in the complex regional pain syndrome affected limb: a case report. *Mol Clin Oncol.* 2021;15.
4. Kasahara S, Niwa SI, Matsudaira K, Sato N, Oka H, Fujii T, Konno SI, Kikuchi SI, Yamada Y. High attention-deficit/hyperactivity disorder scale scores among patients with persistent chronic nonspecific low back pain. *Pain Physician.* 2021; 24:e299-e307.
5. Kasahara S, Takahashi N, Matsudaira K, Oka H, Takatsuki K, Yabuki S. Psychometric properties of the multidimensional pain inventory: Japanese language version (MPI-J). *Pain Physician.* 2021;25:E105-E112.
6. Kasahara S, Matsudaira K, Sato N, Niwa S-I. Pain and attention-deficit/hyperactivity disorder: The case of Margaret Mitchell. *Psychosom Med.* 2021;83:492-493.
7. Mietani K, Hasegawa-Moriyama M, Inoue R, Ogata T, Shimojo N, Kurano M, Sumitani M, Uchida K. Elevated neuron-specific enolase level is associated with postoperative delirium and detection of phosphorylated neurofilament heavy subunit: a prospective observational study. *PLoS ONE.* 2021;16:e0259217.
8. Morita Y, Kariya T, El-Bashir J, Galusca D, Guruswamy J, Tanaka K. TEE image quality improvement with our devised probe cover. *Echocardiography.* 2021;38:1496-1502.
9. Saita K, Sumitani M, Nikaido T, Sekiguchi M, Inoue R, Abe H, Konno S, Uchida K. Exponential correlations among neuropathic components, pain intensity, and catastrophic thoughts in patients with musculoskeletal pain disorder. *Curr Med Res Opin.* 2021;37:1341-1348.
10. Tsuchida R, Tanabe Y, Nishizawa D, Ikeda K, Abe H, Inoue R, Kurano M, Yatomi Y, Tamura K, Takano T, Shimizu C, Uchida K, Sumitani M. Genetic polymorphisms of lysophosphatidic acid receptor 1 are associated with the onset of taxane-induced peripheral neuropathy. *Br J Anaesth.* 2021;127:e43-e46.
11. Uranbileg B, Ito N, Kurano M, Kano K, Uchida K, Sumitani M, Aoki J, Yatomi Y. Inhibition of autotaxin activity ameliorates neuropathic pain derived from lumbar spinal canal stenosis. *Sci Rep.* 2021;11,3984.
12. Yoshimoto T, Fujii T, Oka H, Kasahara S, Kawamata K, Matsudaira K. Pain status and its association with physical activity, psychological stress, and telework among Japanese workers with pain during the COVID-19 pandemic. *Int J Environ Res Public Health.* 2021;18:5595.

Department of Acute Medicine

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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 four 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, otorhino-laryngology 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, with sepsis, with MOF, with shock), post-operative patients, and tertiary emergency patients, placing an emphasis on evidence-based medical therapy.

3) Bed management

The objective of bed management services is to provide a timely and appropriate bed allocation for all the patients. In our hospital, patients are allocated to three types of wards, that is, general ward, ICU2 and ICU/CCU in accordance with their critical condition. The ICU2 undertakes the leading bed management in the hospital to ensure maximum performance as an acute hospital.

4) 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

The topics of lectures for the 2nd year medical student include the prehospital emergency care, the initial evaluation of emergency patients, disaster medicine, serious infections disease, and trauma. Basic Life Support. exercise is also mandatory for the 2nd year medical student.

One month of elective clinical clerkship for the 3rd year. Immediate Cardiac Life Support (ICLS) course is held for the participants in the clinical clerkship program, and successful completion of each course will enable students to be certified as providers.

Clinical integrated lecture for the 4th year students includes diagnosis and treatment of serious patients using case studies of shock, conscious disorder, trauma, intoxication, infections disease, burns, hypothermia, and convulsion. Moreover, after exercise of Advanced Life Support, students experience a real practice of emergency medicine as fellow passengers in the ambulances and as one day trainees in the emergency centers of the affiliated hospitals.

In conformity with the guideline by Ministry of Health, Labor and Welfare, all residents learn and practice emergency medicine and primary care at every level, primary, secondary and tertiary. The residents attend the ICLS course during resident year to obtain the knowledge and skills in CPR.

Junior residents are also assigned to ICU services to gain the knowledge of intensive care from pathophysiological and internal medicine's point of view.

According to the senior resident program in 2006, we train the senior residents to be skilled in advanced critical care medicine including primary care trauma, MOF, shock, and equipment support.

Research activities

Basic research by using the histone injection-induced ARDS model and the ischemia reperfusion injury models on several different organs including intestine and kidney has been conducted to clarify the mechanisms of remote organ injury in multiple organ dysfunction syndrome. 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. Hirayama I, Asada T, Yamamoto M, Hayase N, Hiruma T, Doi K. Changes in carbon dioxide

production and oxygen uptake evaluated using indirect calorimetry in mechanically ventilated patients with sepsis. Crit Care. 2021 Dec 4;25(1): 416.

2. Horie R, Endo Y, Doi K. Estimated glomerular filtration rate may be an independent predictor for clinical outcomes regardless of acute kidney injury complication in the emergency department. PLoS One. 2021 Oct 14;16(10):e0258665.
3. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C,Machado FR, Mcintyre L, Ostermann M, Prescott HC, Schorr C, Simpson S, Joost Wiersinga W, Alshamsi F, Angus DC, Arabi Y, Azevedo L, Beale R, Beilman G, Belley-Cote E, Burry L, Cecconi M, Centofanti J, Yataco AC, De Waele J, Dellinger RP, Doi K, Du B, Estenssoro E, Ferrer R, Gomersall C, Hodgson C, Møller MH, Iwashyna T, Jacob S, Kleinpell R, Klompas M, Koh Y, Kumar A, Kwizera A, Lobo S, Masur H, McGloughlin S, Mehta S, Mehta Y, Mer M, Nunnally M, Oczkowski S, Osborn T, Papathanassoglou E, Perner A, Puskarich M, Roberts J, Schweickert W, Seckel M, Sevransky J, Sprung CL, Welte T, Zimmerman J, Levy M. Executive Summary: Surviving Sepsis Campaign: International Guidelines for the Management of Sepsis and Septic Shock 2021. Crit Care Med. 2021 Nov 1;49(11):1974-1982.
4. 4: Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, Mcintyre L, Ostermann M, Prescott HC, Schorr C, Simpson S, Wiersinga WJ, Alshamsi F, Angus DC, Arabi Y, Azevedo L, Beale R, Beilman G, Belley-Cote E, Burry L, Cecconi M, Centofanti J, Coz Yataco A, De Waele J, Dellinger RP, Doi K, Du B, Estenssoro E, Ferrer R, Gomersall C, Hodgson C, Møller MH, Iwashyna T, Jacob S, Kleinpell R, Klompas M, Koh Y, Kumar A, Kwizera A, Lobo S, Masur H, McGloughlin S, Mehta S, Mehta Y, Mer M, Nunnally M, Oczkowski S, Osborn T, Papathanassoglou E, Perner A, Puskarich M, Roberts J, Schweickert W, Seckel M, Sevransky J, Sprung CL, Welte T, Zimmerman J, Levy M. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021 Nov;47(11):1181-1247.
5. Yamamoto M, Hiruma T, Ueda Y, Doi K. Bilateral mandibular head fractures associated with convulsion. BMJ Case Rep. 2021 Sep 20;14(9):e245713.
6. Ghannoum M, Berling I, Lavergne V, Roberts DM, Galvao T, Hoffman RS, Nolin TD, Lewington A, Doi K, Gosselin S; EXTRIP workgroup. Recommendations from the EXTRIP workgroup on extracorporeal treatment for baclofen poisoning. Kidney Int. 2021 Oct;100(4):720-736.
7. 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.
8. Hirayama I, Doi K, Yamamoto M, Toida C, Morimura N. Evaluation of Autonomous Actions on Bystander-Initiated Cardiopulmonary Resuscitation and Public Access Defibrillation in Tokyo. Int Heart J. 2021 Jul 30;62(4):879-884.
9. Nakamura H, Hirayama I, Hiruma T, Doi K. Subcutaneous injection of organophosphate (Fenitrothion)-Management of preventing the appearance of toxic symptoms: A case report. Clin Case Rep. 2021 Jul ;9(7):e04424.
10. Hirayama I, Inokuchi R, Fukue M, Doi K. Giant hepatic cyst causing lower extremity edema and scoliosis. Clin Case Rep. 2021 Feb 22;9(4):2483-2484.
11. Fukushima K, Inokuchi R, Hirayama I, Hiruma T, Doi K. Early diagnosis and antibiotic treatment for fulminant Clostridium difficile infection. Clin Case Rep. 2020 Dec 7;9(2):729-731.

Health Sciences and Nursing

1. Health Sciences

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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."

The department currently has faculty members introduced above, an associate professor, a project lecturer, a research associate, part-time lecturers, a technical specialist, visiting research fellows, 5 doctoral course students, 6 master course students, and secretaries.

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 and psychosocial support and provides education/ training of professionals in related fields from global perspectives. The World Mental Health Japan survey, which is part of a WHO international collaboration, is a largest epidemiologic study of common mental disorders in the community in Japan. Assessment of health effects of job stressors and effectiveness of interventions to reduce job stress are also core research activities of the department. Current issues around occupational mental health (e.g., intervention program using Internet-based cognitive behavioral therapy) are also actively investigated. Furthermore, research in the department includes various other topics, such as perinatal mental health, traumatic stress and resilience, supporting rehabilitation and recovery of people with chronic mental illness, suicide prevention, social disparity in mental health, disaster mental health, and global mental health. Most of the research has been conducted in a close collaboration with researchers in other domestic and foreign institutions/universities.

References

1. Iida, M, Watanabe, K, Imamura, K, Sakuraya, A, Asaoka, H, Sato, N, Nozawa, K, & Kawakami, N. Development and validation of the Japanese version of the team job crafting scale for nurses. Research in Nursing & Health 44.2, 2021: 329-343.
2. Iida, M, Sasaki, N, Kuroda, R, Tsuno, K, & Kawakami, N. Increased COVID-19-related workplace bullying during its outbreak: a 2-month prospective cohort study of full-time employees in Japan. Environmental and Occupational Health Practice, 2021.
3. Asaoka H, Sasaki N, Kuroda R, Tsuno K, Kawakami N. Workplace Bullying and Patient Aggression Related to COVID-19 and its Association with Psychological Distress among Health Care Professionals during the COVID-19 Pandemic in Japan. Tohoku J Exp Med. 2021; 255(4):283-289.
4. Asaoka H, Sasaki N, Imamura K, Kuroda R, Tsuno K, Kawakami N. Changes in COVID-19 measures in the workplace: 8-month follow-up in a cohort study of full-time employees in Japan. J Occup Health. 2021 Jan;63(1):e12273.
5. Imamura K, Tran TTT, Nguyen HT, Sasaki N, Kuribayashi K, Sakuraya A, Bui TM, Nguyen AQ, Nguyen QT, Nguyen NT, Nguyen KT, Nguyen GTH, Tran XTN, Truong TQ, Zhang MW, Minas H, Sekiya Y, Watanabe K, Tsutsumi A, Kawakami N. Effect of smartphone-based stress management programs on depression and anxiety of hospital nurses in Vietnam: a three-arm randomized controlled trial. Sci Rep. 2021 May 31;11(1):11353.
6. Yang CC, Watanabe K, Kawakami N. The Associations between Job Strain, Workplace PERMA Profiler, and Work Engagement. J Occup Environ Med. 2021 Dec 6.
7. Watanabe K, Kawakami N. Association between sitting time at work and the onset of major depressive episode: a 1-year prospective cohort study using the Bayesian regression. BMC Public Health. 2021 Oct 29;21(1):1960.
8. Kawakami N, Imamura K, Watanabe K, Sekiya Y, Sasaki N, Sato N; SMART-CBT Project Team. Effectiveness of an Internet-Based Machine-Guided Stress Management Program Based on Cognitive Behavioral Therapy for Improving Depression Among Workers: Protocol for a Randomized Controlled Trial. JMIR Res Protoc. 2021 Sep 29;10(9):e30305.
9. Sato N, Watanabe K, Kawakami N. Mediating Effects of Work Eudemonic Well-being for the Association Between Psychosocial Work Environment and Overall Eudemonic Well-being Among Japanese Workers: A Cross-sectional Study. J Occup Environ Med. 2021 Aug 1;63(8): e542-e548.
10. Sato N, Watanabe K, Nishi D, Kawakami N. Associations Between Personal Values and Work Engagement: A Cross-Sectional Study Using A Representative Community Sample. J Occup Environ Med. 2021 Jun 1;63(6):e335-e340.
11. de Vries YA, Harris MG, Vigo D, Chiu WT, Sampson NA, Al-Hamzawi A, Alonso J, Andrade LH, Benjet C, Bruffaerts R, Bunting B, Caldas de Almeida JM, de Girolamo G, Florescu S, Gureje O, Haro JM, Hu C, Karam EG, Kawakami N,

Kovess-Masfety V, Lee S, Moskalewicz J, Navarro-Mateu F, Ojagbemi A, Posada-Villa J, Scott K, Torres Y, Zarkov Z, Nierenberg A, Kessler RC, de Jonge P; WHO World Mental Health Survey collaborators. Perceived helpfulness of treatment for specific phobia: Findings from the World Mental Health Surveys. J Affect Disord. 2021 Jun 1;288:199-209.

12. Yang CC, Lee KW, Watanabe K, Kawakami N. The association between shift work and possible obstructive sleep apnea: a systematic review and meta-analysis. Int Arch Occup Environ Health. 2021 Nov;94(8):1763-1772.
13. Kawakami N, Sasaki N, Kuroda R, Tsuno K, Imamura K. The Effects of Downloading a Government-Issued COVID-19 Contact Tracing App on Psychological Distress During the Pandemic Among Employed Adults: Prospective Study. JMIR Ment Health. 2021 Jan 12;8(1): e23699.
14. Sasaki N, Yasuma N, Obikane E, Narita Z, Sekiya J, Inagawa T, Nakajima A, Yamada Y, Yamazaki R, Matsunaga A, Saito T, Imamura K, Watanabe K, Kawakami N, Nishi D. Psycho-educational interventions focused on maternal or infant sleep for pregnant women to prevent the onset of antenatal and postnatal depression: A systematic review. Neuropsychopharmacol Rep. 41(1):2-13, 2021
15. Wu Y, Levis B, Ioannidis JPA, Benedetti A, Thombs BD; DEPRESSion Screening Data (DEPRESSD) Collaboration (Nishi D, 156/232). Probability of Major Depression Classification Based on the SCID, CIDI, and MINI Diagnostic Interviews: A Synthesis of Three Individual Participant Data Meta-Analyses. Psychother Psychosom. 90(1):28-40, 2021
16. Yasuma N, Imamura K, Watanabe K, Nishi D, Kawakami N, Takano A. Association between energy drink consumption and substance use in adolescence: A systematic review of prospective cohort studies. Drug Alcohol Depend. 219: 108470, 2021
17. Sasaki N, Imamura K, Nishi D, Watanabe K, Sekiya Y, Tsuno K, Kobayashi Y, Kawakami N. Internet-based acceptance and commitment therapy programme 'Happiness Mom' for well-being: a protocol for a randomised controlled trial. BMJ Open. 26;11(2): e042167, 2021
18. Yasuma, N, Yamaguchi, S, Ogawa, M, Shiozawa T, Abe M, Igarashi M, Kwaguchi T, Sato S, Nishi D, Kawakami N, Fujii C. Care difficulties and burden during COVID‐19 pandemic lockdowns among caregivers of people with schizophrenia: A cross‐sectional study. Neuropsychopharmacol Rep. 41(2):242-247, 2021
19. Kataoka M, Nishi D. Association between Work-Related Trauma Exposure and Posttraumatic Stress Symptoms among Child Welfare Workers in Japan: A Cross-Sectional Study. International Journal of Environmental Research and Public Health. 18(7):3541, 2021
20. Bhandari PM, Levis B, Neupane D, Patten SB, Shrier I, Thombs BD, Benedetti A, and the DEPRESSion Screening Data (DEPRESSD) EPDS Group (Nishi D, 57/82). Data-driven methods distort optimal cutoffs and accuracy estimates of depression screening tools: a simulation study using individual participant data. Journal of Clinical Epidemiology. 137:137-147, 2021
21. Obikane E, Baba T, Shinozaki T, Obata S, Nakanishi S, Murata C, Ushio E, Suzuki Y, Shirakawa N, Honda M, Sasaki N, Nishi D, O'Mahen H, Kawakami N. Internet-based behavioural activation to improve depressive symptoms and prevent child abuse in postnatal women (SmartMama): a protocol for a pragmatic randomized controlled trial. BMC Pregnancy Childbirth 21:314, 2021
22. Nangaku M, Kadowaki T, Yotsuyanagi H, Ohmagari N, Egi M, Sasaki J, Sakamoto T, Hasegawa Y, Ogura T, Chiba S, Node K, Suzuki R, Yamaguchi Y, Murashima A, Ikeda N, Morishita E, Yuzawa K, Moriuchi H, Hayakawa S, Nishi D, Irisawa A, Miyamoto T, Suzuki H, Sone H, Fujino Y. The Japanese Medical Science Federation COVID-19 Expert Opinion English Version. JMA J. 15;4(2):148-162, 2021
23. Nakao T, Murayama K, Takahashi S, Kayama M, Nishi D, Horinouchi T, Oya N, Kuga H. Mental Health Difficulties and Countermeasures during the Coronavirus Disease Pandemic in Japan: A Nationwide Questionnaire Survey of Mental

Health and Psychiatric Institutions. Int J Environ Res Public Health. 8;18(14):7318, 2021

24. Stein DJ, Kazdin AE, Ruscio AM, Chiu WT, Sampson NA, Ziobrowski HN, Aguilar-Gaxiola S, Al-Hamzawi A, Alonso J, Altwaijri Y, Bruffaerts R, Bunting B, de Girolamo G, de Jonge P, Degenhardt L, Gureje O, Haro JM, Harris MG, Karam A, Karam EG, Kovess-Masfety V, Lee S, Medina-Mora ME, Moskalewicz J, Navarro-Mateu F, Nishi D, Posada-Villa J, Scott KM, Viana MC, Vigo DV, Xavier M, Zarkov Z, Kessler RC; WHO World Mental Health Survey collaborators. Perceived helpfulness of treatment for generalized anxiety disorder: a World Mental Health Surveys report. BMC Psychiatry. 21(1): 392, 2021
25. Sasaki N, Carrozzino D, Nishi D. Sensitivity and concurrent validity of the Japanese version of the Euthymia scale: a clinimetric analysis. BMC Psychiatry. 4;21(1):482, 2021.
26. Sasaki N, Obikane E, Vedanthan R, Imamura K, Cuijpers P, Shimazu T, Kamada M, Kawakami N, Nishi D. Development and Validation of Implementation Outcome Scales for Digital Mental Health (iOSDMH). JMIR Formative Research 23;5(11):e24332, 2021
27. Roest AM, de Vries YA, Al-Hamzawi A, Alonso J, Ayinde O, Bruffaerts R, Bunting B, Caldas-de-Almeida, JM, de Girolamo G, Degenhardt L, Florescu S, Gureje O, Haro JM, Hu CY, Karam EG, Kiejna A, Kovess-Masfety V, Lee S, McGrath JJ, Medina-Mora ME, Navarro-Mateu F, Nishi D, Piazza M, Posada-Villa J, Scott KM, Stagnaro JC, Stein DJ, Torres Y, Viana MC, Zarkov Z, Kessler RC, de Jonge P, on behalf of the WHO World Mental Health Survey collaborators. Previous disorders and current impairment and suicidality in individuals with 12-month major depressive disorder in the World Mental Health surveys. Epidemiology and Psychiatric Sciences 11;30:e70, 2021
28. Asaoka H, Koido Y, Kawashima Y, Ikeda M, Miyamoto Y, Nishi D. Longitudinal change in depressive symptoms among healthcare professionals with and without COVID-19 vaccine hesitancy from October 2020 to June 2021 in Japan. Industrial Health (Epub ahead of print)
29. Sasaki N, Akiyama H, Kawakami N, Nishi D. Preconception menstrual cycle disorder and antenatal depression: A cross-sectional study with pre-recorded information. J Psychosom Obstet Gynaecol. (Epub ahead of print)
30. Asaoka H, Koido Y, Kawashima Y, Ikeda M, Miyamoto Y, Nishi D. Longitudinal Change of Psychological Distress among Healthcare Professionals with and without Psychological First Aid Training Experience during the COVID-19 Pandemic. International Journal of Environmental Research and Public Health. 18(23):12474, 2021
31. Mascayano F, van der Ven E, Moro MF, Schilling S, Alarcón S, Barathie JA, Alnasser L, Asaoka H, Ayinde O, Balalian AA, Basagoitia A, Brittain K, Dohrenwend B, Durand–Arias S, Eskin M, Fernández–Jiménez E, Freytes M, Giménez L, Gisle L, Hoek HW, Jaldo R, Lindert J, Maldonado H, Martínez -Alés G, Martínez -Viciana C, Mediavilla R, McCormack C, Myer L, Narvaez J, Nishi D, Ouali U, Puac-Polanco V, Ramírez J, Restrepo-Henao A, Rivera -Segarra E, Rodríguez AM, Saab D, Seblova D, Tenorio A, Valeri L, Alvarado R, Susser E, On behalf of the HEROES group. The impact of the COVID-19 pandemic on the mental health of healthcare workers: study protocol for the COVID-19 HEalth caRe wOrkErS (HEROES) study. Social Psychiatry and Psychiatric Epidemiology (in press)
32. Hidaka Y, Imamura K, Watanabe K, Tsutsumi A, Shimazu A, Inoue A, Hiro H, Odagiri Y, Asai Y, Yoshikawa T, Yoshikawa E. Associations between work-related stressors and QALY in a general working population in Japan: a cross-sectional study. International Archives of Occupational and Environmental Health. 2021 May 30:1-9.
33. Hidaka Y, Sasaki N, Imamura K, Tsuno K, Kuroda R, Kawakami N. Changes in fears and worries related to COVID-19 during the pandemic among current employees in Japan: a 5-month longitudinal study. Public health. 2021 Sep 1;198:69-74.
34. Hidaka Y, Watanabe K, Imamura K, Tatha O, Kawakami N. Reliability and validity of the

Chinese version of the New Brief Job Stress Questionnaire (New BJSQ) among workers in China. Industrial health. 2021 Nov 1.

35. Komase Y, Watanabe K, Hori D, Nozawa K, Hidaka Y, Iida M, Imamura K, Kawakami N. Effects of gratitude intervention on mental health and well-being among workers: A systematic review. Journal of Occupational Health, 2021;63: e12290.
36. Yasuma, N., Nishi, D., Watanabe, K., Ishikawa, H., Tachimori, H., Takeshima, T., . . . Kawakami, N. (2021). Association between Urban Upbringing and Compulsive Internet Use in Japan: A Cross-Sectional, Multilevel Study with Retrospective Recall. Int J Environ Res Public Health, 18(18), 9890.
37. Komase Y, Watanabe K, Natsu S, Kawakami N. The effect of perceived gratitude from others on work engagement: a cross-sectional study. Journal of Occupational and Environmental Medicine. 2021;63:e592-e595.
38. Yasuma N, Yamaguchi S, Ogawa M, et al. Care difficulties and burden during COVID‐19 pandemic lockdowns among caregivers of people with schizophrenia: A cross‐sectional study. Neuropsychopharmacol Rep. 2021; 00: 1‐7.
39. Komase Y, Watanabe K & Kawakami N. Effects of a gratitude intervention program on work engagement among Japanese workers: a protocol for a cluster randomized controlled trial. BMC Psychol 9, 35 (2021).
40. Yasuma N, Watanabe K, Nishi D, Ishikawa H, Tachimori H, Takeshima T, Umeda M and Kawakami N (2021) Psychotic Experiences and Hikikomori in a Nationally Representative Sample of Adult Community Residents in Japan: A Cross-Sectional Study. Front. Psychiatry 11: 602678.

Department of Biostatistics/ Epidemiology and Preventive Health Sciences

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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 (current EP-CRSU, Co., Ltd.) 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 through the aforementioned J-CRSU (a non-profit organization), 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. Ebata S, Yoshizaki A, Oba K, Kashiwabara K, Ueda K, Uemura Y, Watadani T, Fukasawa T, Miura S, Yoshizaki-Ogawa A, Asano Y, Okiyama N, Kodera M, Hasegawa M, Sato S. Safety and efficacy of rituximab in systemic sclerosis: a double-blind, parallel-group comparison, investigators initiated confirmatory clinical trial (DESIRES). Lancet Rheumatol. 2021;3:E489–E497.
2. Kuwabara M, Oba K, Takano N, Nagamine N, Maruyama Y, Ito N, Watanabe I, Ikeda C,

Sakamoto J. An exploratory questionnaire survey about overwork on mental health of Japanese elementary and junior high school teachers. J Ment Health Train Educ Pract 2021;16:181–186.
3. Ota K, Oba K, Fukui K, Ito Y, Hamada E, Mori N, Oka M, Ota K, Shibata Y, Takasu A. Sites of blood collection and topical antiseptics associated with contaminated cultures: prospective observational study. Sci Rep. 2021;11:6211.
4. Takeuchi Y, Kumamaru H, Hagiwara Y, Matsui H, Yasunaga H, Miyata H, Matsuyama Y. Sodium-glucose cotransporter-2 inhibitors and the risk of urinary tract infection among diabetic patients in Japan: Target trial emulation using a nationwide administrative claims database. Diabetes Obes Metab. 2021;23:1379–1388.
5. Yamada G, Hagiwara Y, Kimura T, Takeuchi Y, Oba K, Masuda K, Matsuyama Y. Impact of body weight gain on the incidence of non-alcoholic fatty liver disease in non-obese Japanese individuals. Am J Gastroenterol. 2021;116:733–740.
6. Sasaki S, Nagasaki T, Oba K, Akiyoshi T, Mukai T, Yamaguchi T, Fukunaga Y, Fujimoto Y. Risk factors for outlet obstruction after laparoscopic surgery and diverting ileostomy for rectal cancer. Surg Today. 2021;51:366–373.
7. Hagiwara Y, Shinozaki T, Mukai H, Matsuyama Y. Sensitivity analysis for subsequent treatments in confirmatory oncology clinical trials: a two-stage stochastic dynamic treatment regime approach. Biometrics. 2021;77:702–714.
8. Kozuma K, Kozuma K, Shinozaki T, Kashiwabara K, Oba K; Xience P. M. S. Group; PROMUS Element/Element Plus P. M. S. Group, Matsuyama Y. Multivariable Prediction Model to Estimate the Probability of Restenosis at Proximal Edge After 2nd-generation Drug-Eluting-Stent Implantation: Development and Internal Validation Using a Quantitative Coronary Angiography From the Post-Marketing Surveillance Studies of Everolimus-Eluting Stent in Japan. Cardiovasc Interv Ther. 2021;36:190–197.
9. Fuyama K, Hagiwara Y, Matsuyama Y. A simulation study of regression approaches for estimating risk ratios in the presence of multiple confounders. Emerg Themes Epidemiol. 2021;18:18.
10. Ito C, Hashimoto A, Uemura K, Oba K. Misleading Reporting (Spin) in Noninferiority Randomized Clinical Trials in Oncology With Statistically Not Significant Results: A Systematic Review. JAMA Netw Open. 2021;4:e2135765.
11. Ota K, Oba K, Ito Y, Cheng J, Ota K, Takasu A. Focused Assessment with Sonography for Trauma (FAST) training for first-year resident physicians at a university hospital in Japan: A longitudinal, observational study. SAGE Open Medicine. 2021;9:20503121211044367.
12. Takeuchi Y, Ogawa M, Hagiwara Y, Matsuyama Y. Non-parametric approach for frequentist multiple imputation in survival analysis with missing covariates. Stat Methods Med Res. 2021;30:1691–1707.
13. Hagiwara Y, Sawaki M, Uemura Y, Kawahara T, Shimozuma K, Ohashi Y, Takahashi M, Saito T, Baba S, Kobayashi K, Mukai H, Taira N. Impact of chemotherapy on cognitive functioning in older patients with HER2-positive breast cancer: a sub-study in the RESPECT trial. Breast Cancer Res Treat. 2021;188:675–683.
14. Chamseddine AN, Oba K, Buyse M, Boku N, Bouché O, Satar T, Auperin A, Paoletti X. Impact of follow-up on generalized pairwise comparisons for estimating the irinotecan benefit in advanced/metastatic gastric cancer. Contemp Clin Trials. 2021;105:106400.
15. Kawaguchi Y, Hasegawa K, Hagiwara Y, De Bellis M, Famularo S, Panettieri E, Matsuyama Y, Tateishi R, Ichikawa T, Kokudo T, Izumi N, Kubo S, Sakamoto M, Shiina S, Takayama T, Nakashima O, Murakami T, Vauthey JN, Giuliante F, De Carlis L, Romano F, Ruzzenente A, Guglielmi A, Kudo M, Kokudo N. Effect of diameter and number of hepatocellular carcinomas on survival after resection, transarterial chemoembolization, and ablation. Am J Gastroenterol. 2021:116;1698–1708.

(Only main publications)

Department of Biomedical Ethics & Department of Health Promotion Sciences

Professor

Akira Akabayashi, M.D., Ph.D.

Associate Professor

Yoshiyuki Takimoto, M.D., Ph.D.

Lecturer

Eisuke Nakazawa, Ph.D.

Research Associate

Makoto Udagawa, MA

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. 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 a

professor, an associate professor, a lecturer, an associate, and a technical specialist. All five members, twoproject researchers, eleven lecturers from other organizations, and seven visiting researchers contribute to department teaching and research activities.

We have eight department graduate students. Five 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. Eighteen bachelor theses, twenty-two master theses, and eleven doctoral dissertations were completed between April 2004 and March 2020. 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)
13) Global Bioethics (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.cbel.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. Ino H, Nakazawa E, Akabayashi A. Drug repurposing for COVID-19: Ethical considerations and roadmaps. Camb Q Healthc Ethics. 2021;30:51-58. doi:10.1017/S0963180120000481.
2. Kubota S, Nakazawa E. Concept and implications of sexual consent for education: A systematic review of empirical studies. Sex Relation Ther. Published online first on February 15, 2022. doi:10.1080/14681994.2022.2039617.
3. Kurisu K, Yamanaka Y, Yamazaki T, Yoneda R, Otani M, Takimoto Y, Yoshiuchi K. A clinical course of a patient with anorexia nervosa receiving surgery for superior mesenteric artery syndrome. J Eat Disord. 2021 Jun 30;9(1):79. doi:10.1186/s40337-021-00436-2.
4. Nakazawa E, Akabayashi A. Citizen and patient participation in precision medicine: Epilepsy treatment using brain organoids derived from iPS cells. AJOB Neurosci 2022;13(2):138-140. doi: 10.1080/21507740.2022.2048737.
5. Nakazawa E, Akabayashi A. Covid-19, global ethics, and Jihi: A voice from East Asian philosophy. Indian J Med Ethics. 2021;6(2):138-139. doi:10.20529/IJME.2020.126.
6. Nakazawa E, Akabayashi A. Unauthorized Immigrants in Japan Facing the COVID-19 Pandemic. Journal of Seizon and Life Sciences. 2021;32(1):75-88.
7. Nakazawa E, Yamamoto K, London AJ, Akabayashi A. Solitary death and new lifestyles during and after COVID-19: wearable devices and public health ethics. BMC Med Ethics. 2021; 22:89. doi:10.1186/s12910-021-00657-9.
8. Ohsawa M, Makino T, Takimoto Y, Inui A. Application of Kampo medicines for the palliation of cancer cachexia. Neuropeptides. 2021 Dec;90:102188. doi: 10.1016/j.npep.2021.102188.
9. Takimoto Y. Should suicide be prevented among cancer patients? Palliat Support Care. 2021 Mar 10;1-2. doi:10.1017/S1478951521000249.

Health Sciences and Nursing

2. Preventive and Administrative Nursing

Department of Nursing Administration / Advanced Clinical Nursing

Associate Professor

Yukie Takemura, Ph.D., R.N., C.N.A.

Assistant Professor

Naoko Ichikawa, Ph.D., R.N.

Ryohei Kida, Ph.D., R.N.

Tamaki Isobe, Ph.D., R.N

Project Assistant Professor

Satoko Nagai, MSN, R.N. (2021.9~)

Homepage http://nurs-adm.umin.jp/

Introduction and Organization

The Department of Nursing Administration / Advanced Clinical Nursing has 60 years of history and tradition. It was first established in 1954 as the Department of Fundamental Nursing at the School of Health Care and Nursing. The School of Health Care and Nursing was composed of two basic medical departments and six nursing departments. When it was reorganized as the School of Health Sciences in 1965, only one nursing department remained. Renamed the Department of Nursing, it was responsible for nursing education. In 1992, the School of Health Sciences became the School of Health Sciences and Nursing, and two new departments of nursing were established; the Department of Nursing then became the Department of Fundamental Nursing. As a result of the shift to the chair of the Graduate School of Medicine in 1996, two departments were established: the Department of Nursing Administration and the Department of Advanced Clinical Nursing. Our department is responsible for undergraduate fundamental nursing education.

Teaching activities

Undergraduate Courses

In the undergraduate program, our department oversees lectures and clinical practicums for Introduction to Nursing Science, Fundamental Nursing I, Fundamental Nursing II, Basic Nursing Skills, and Nursing Administration.

Introduction to Nursing Science (1 credit, lecture)

In this course, students learn nursing concepts, functions, theories, targets, and the practical side of nursing through lectures, discussions, and inter-professional education.

Theory and Methodology of Nursing I (2 credits, lecture)

This course provides knowledge and nursing skills for understanding patients and providing care. Students learn about the nursing process and skills necessary for knowing and caring for patients, which are essential for providing appropriate nursing care.

Theory and Methodology of Nursing II (2 credits, elective course, lecture)

This course offers perspectives on the nursing

profession through a series of lectures from various experts and discussions.

Basic Nursing Skills (2 credits, lecture)

This course covers the basics of assessing clients' health, including physical examination skills and practices in fundamental nursing skills, which are essential for providing nursing care with physiological and psychosocial integrity. Students learn about the nursing process through case discussions.

Practicum: Basic Nursing Skills

(2 credits, practicum)

Under instructors' supervision, students have the opportunity to apply their fundamental knowledge and nursing skills in a variety of settings. Students will assess clients' health and needs by applying the nursing process.

Nursing Administration (1 credit, lecture)

This course introduces students to the roles of nurse administrators/managers in all types of healthcare settings, such as institutions, organizations, and communities as well as political settings. Students will learn the fundamental theories and practices of nursing administration/management by analyzing current issues in healthcare and nursing.

Practicum: Nursing Administration

(1 credit, practicum)

Students participate in a nursing administrative practicum in units or divisions in hospitals. They will learn about care delivery systems, such as staffing and patient classification systems, nursing informatics, and budgetary issues (e.g., cost effectiveness and quality improvement).

Graduate Courses

In the graduate program, our department oversees lectures and seminars for Nursing Administration and Advanced Clinical Nursing.

Nursing Administration I (2 credits)

During this course, students acquire the necessary knowledge and perspectives to become actively involved in an organization and to conduct research that focuses on organizational phenomena through lectures on and a critical analysis of relevant organizational and human resource management theories, the environment surrounding nursing science and nursing practice, and political decision making.

Seminar

We have an accredited departmental seminar where members discuss their own research project plans.

Research activities

We aim to clarify the systems and methodologies that fulfil the organizational and human resource potential to contribute to the wellbeing of patients, nurses, and other healthcare professionals as well as society in general.

Development of Research Methods for Depicting Organizational Phenomena

Careful extraction and accumulation of knowledge from organizational case studies is necessary to develop nursing administrators and contribute to clinical practice. For this reason, when analyzing such cases, we clarify phenomena shared across individuals and facilities in multiple cases and develop research methods to vividly describe dynamic and complex workplace-related and organizational processes. For instance, we examine workplace experiences based on studies of multiple organizations and describe organizational management processes based on the experiences of those providing and receiving support.

Discovering Knowledge Required for Effective Organizational Management and Development

It is important that workers, including nursing administrators, use their abilities to the fullest and function effectively to provide quality care to patients, families, and society in general. We engage in research that clarifies the key elements and processes involved. Concrete examples include investigating nursing organizational operation models during times of crisis, based on case studies following the 2011 earthquake and tsunami in Fukushima, case study of medical facilities that systematically work to improve the workplace environment for nurses, as well as exploring connections between nursing managers' competencies and leadership and staff development, professional commitment, on-the-job behavior, job satisfaction, workplace culture, and employee turnover rates.

Creating Workplaces Where Staff and Teams Can Demonstrate Their Abilities

We engage in research that contributes to the creation of workplaces where staff and teams can demonstrate their latent abilities to the fullest. This includes supporting individuals and teams, organizational development, and the improvement of individuals and team environments. Concrete examples include organizational learning, intra-organizational communication and roles, diversity climate in nursing organizations, and person-environment fit in nurses.

Creating Mechanisms that Sustainably Provide High-Quality Medical Care and Nursing

We engage in research that contributes to the creation of sustainable organizations and care environments, including securing nursing human resources, maintaining the quality of such resources, and creating systems in organizational environments. Examples include research investigating the development of nursing careers and professional expertise, returning to work in the nursing profession, the nursing labor market, and impact of nursing turnover on the organization.

References

1. Ishii K, Takemura Y, & Ichikawa, N. Relationships between the components of nurse managers' transformational leadership and organizational learning subprocesses in a hospital ward: A cross-sectional study. Journal of Nursing Management. 2021; 29(4); 672-680.
2. Inoue M, Kunie K, Takemura Y, Ichikawa N, & Kida R. The influence of learning circumstances and on-the-job opportunities for professional growth on perceived person-environment fit among hospital nurses: A longitudinal study. Journal of Nursing Management. 2021; 29(4); 776-784
3. Saiki M, Kunie K, & Takemura Y. Nursing assistants' desired roles, perceptions of nurses' expectations, and effect on team participation: A cross-sectional study. Journal of Nursing Management. 2021; 29(5); 1046-1053.
4. Kida R & Takemura Y. Strategies at health care facilities to improve working environment for Japanese nursing staff: Multiple case study. The Journal of the Japan Academy of Nursing Administration and Policies. 2021; 25(1); 20-33. [in Japanese]
5. Komagata M, Takemura Y, Ichikawa N, Takehara K, & Kunie K. Reliability and validity of the Japanese version of the job characteristics scale among nurses. The Journal of the Japan Academy of Nursing Administration and Policies. 2021; 25(1); 12-19. [in Japanese]
6. Piao X, Tsugawa S, Takemura Y, Ichikawa N, Kida R, Kunie K, Managi S. Disability Weights Measurement for 17 Diseases in Japan: A Survey Based on Medical Professionals. Economic Analysis and Policy. 2021; 70; 238-248
7. Takahashi Y, Kunie K, & Takemura Y. The lasting impacts of work-attendance decisions of health care employees under uncertainty: Japanese hospital nurses' experiences outside the evacuation zone after the nuclear accident. Journal of Organization and Discourse. 2021; 2(1); 9-19.
8. Tanaka S, Kunie K, Takemura Y, Ichikawa N, & Kida R. Exploring nurses' clinical reasons for bed transfers in acute care wards: An observational study. Journal of Nursing Management, 2021; 29(7); 2297-2306.
9. Kawaguchi S, Takemura Y, Takehara K, Kunie K, Ichikawa N, Komagata K, Kobayashi K, Soma M, & Komiyama C. Relationship between teams' Leader–Member Exchange characteristics and psychological outcomes for nurses and nurse managers: A cross-sectional study in Japan. Sage Open Nursing, 2021; 7: 1-11.
10. Tanaka S, Kunie K, Takemura Y, Ichikawa N, & Kida R. The patterns and reasons for changing bed placement in multi-bed rooms in acute care settings. Journal of Society of Nursing Practice 2021; 33(3): 11-23.
11. Ishii K, Takemura Y, Ichikawa N, Kunie K, Kida R. The relationship between nursing groups' organizational socialization and nurses' perception of organizational learning subprocesses: a cross-sectional study in hospital wards. Team Performance Management: An International Journal. 2021 Aug 16.
12. Inoue M, Kunie K, Takemura Y, Ichikawa N, & Kida R. Development of a Japanese version of perceived fit scale to measure perceived

multidimensional person-environment fit: Validity and reliability tests among nurses. Journal of Japan Academy of Nursing Science. 2021;41:692-700. [in Japanese]

13. Saiki M, Takemura Y, & Kunie K. Development and evaluation of an intervention program for nurses and nursing assistants to recognize the roles of nursing assistants. Journal of Japan Academy of Nursing Science. 2021;41:638-46. [in Japanese]

Department of Family Nursing

Professor

Mari Ikeda, Ph.D., R.N., R.C.P.

Lecturer

Iori Sato, Ph.D., R.N., P.H.N.

Assistant Professors

Mayumi Morisaki, Ph.D., R.N., P.H.N.

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 is 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 Practinum 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. QOL for cancer patients and their families;
4. Development of a Pediatric Quality of Life (QOL) Inventory for children with chronic illness and their parents;
5. Lifetime support for survivors of childhood cancer and their families: treatment and care in their late effects, special needs education, and working;
6. Transitional care for children, adolescent and young adult with childhood-onset chronic diseases;
7. Research about prevention of deterioration of postpartum depression, child abuse and neglect;
8. 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 Bifilco 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.

Studies on “Development of a Pediatric Quality of Life (QOL) Inventory for children with chronic illness and their parents” and “Lifetime support for survivors of childhood cancer and their families: treatment and care in their late effects, special needs education, and working” have been ongoing, in collaboration with pediatric cancer researchers and a variety of family support organizations across the country. Funding for these research projects was granted through a 2004-2006 Ministry of Education, Culture, Sports, Science and Technology Grant-in-Aid for Scientific Research, and currently through a Practical Research for Innovative Cancer Control (AMED) and a 2014-2016 Ministry of Education, Culture, Sports, Science and Technology Grant-in-Aid for Scientific Research. Based on the department’s rich collective research experiences, we founded the Center for Quality-of-Life Research in April 2012 to study QOL across wide developmental stages and health conditions. Using this platform, we aim to accumulate, integrate, and disseminate scientific research and knowledge on QOL in a more systematic manner.

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. Nakahachi T, Ishii R, Canuet L, Sato I, Kamibeppu K, Ueda M, Ueno K, Iwase M. Influence of mood states on the correlation between changes in oxygenated hemoglobin concentration and behavioral performance during Tetris gameplay in the frontal cortex. Cognition & Rehabilitation. 2021; 2(1): 128-30.
2. Kita S, Sato I, Sakka M, Soejima T, Kamibeppu K. Does the use of childcare services reduce the impact of intimate partner violence on the quality of life of children?: Multiple-group structural equation modeling. Applied Research in Quality of Life. 2021; 16: 1825-45.
3. Morisaki-Nakamura M, Suzuki S, Kobayashi A, Kita S, Sato I, Iwasaki M, Hirata Y, Sato A, Oka A, Kamibeppu K. Development and validation of a Japanese version of the Transition-Q. Pediatrics International. 2021; 63, 270-8.
4. Sakka M, Kita S, Sato I, Soejima T, Eguchi H, Tokita M, Yamamoto-Mitani N, Shimazu A, Kamibeppu K. Reliability and validity of the Japanese version of the Caregiving Interface Work Scale in employed Japanese family caregivers. Geriatrics & Gerontology International. 2021; 21: 254-61.
5. Sakai S, Nagae H, Miyashita M, Harasawa N, Iwasaki T, Katayama Y, Takenouchi S, Ikeda M, Ito M, Tamura K. Developing an instrument to assess the readiness for advance care planning. Journal of Pain and Symptom Management. 2021:, 63(3): 374-386

Department of Community Health Nursing / Public Health Nursing

Professor (concurrent)

Noriko Yamamoto-Mitani, Ph.D., R.N., P.H.N.

Lecturer (~May, 2021)

Takashi Naruse, Ph.D., R.N., P.H.N.

Assistant Professor

Riho Iwasaki, Ph.D., R.N., P.H.N.

Chikako Honda, Ph.D., R.N., P.H.N.

Yuka Sumikawa, Ph. Ph.D., R.N., P.H.N.

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Introduction and Organization

Department of Community Health Nursing was established in June 1992. Department of Public Health Nursing was established related to opening of master course for public health nurses in 2006. In addition, program for public health nurse license was started in 2014, and our department is in charge of it.

Teaching activities

In the undergraduate program, we lecture about fundamental methodologies and theories of health promotion for individuals, families, and specific populations living in the community. The titles are below; Home Health Nursing, Community Health Nursing, Home Health Nursing Practice. There is a total of four credits of lectures and two credits of nursing placement training.

In the graduate program, we lecture about the advanced methodologies and theories in community health nursing and public health nursing. The titles are below; Advanced Community Health Nursing I, Advanced Community Health Nursing II, Advanced Community Health Nursing Seminar I, II and Practice I, II. There are a total of 12 credits: 4 credits of lectures and 8 credits of exercises and practical training.

We also provide additional eight kinds of lectures/ practical training as a part of the education program for public health nurse licenses. The titles are below; Skills for Public Health Nursing I, Skills for Public Health Nursing II, Public Health Nursing I, Public Health Nursing II, Public Health Nursing III, Public Administration for Nurses, Public Health Nursing Practice I, Public Health Nursing Practice II. There are 12 credits of lectures and five credits of practical training.

And we also assist undergraduate/graduate students with their thesis.

Research activities

Our research focuses on the development and evaluation of health care programs, establishment of

community health care systems, and standardization of skills among public health nurses in response to the health care needs of individuals, families, aggregates and communities. Our research is supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Health Science research, and other foundations.

Ongoing research projects in our department are listed below.

1. Developing a community care system and fostering collaboration between home-care service providers.
Fostering collaboration between home-care service providers is an international concern in community care, especially elderly health care. We are conducting a study to measure the status of collaboration between care providers in a community setting; it also aims to develop efficient and feasible strategies to improve this status.

2. Discharge planning
Discharge planning is an interdisciplinary process that is ideally available to aid patients and their families in developing a feasible plan for the next step of care. Demand for discharge planning is increasing. We are attempting to standardize discharge planning activities and develop outcome indicators and an educational program on discharge planning for ward nurses. We are also conducting research on the discharge planning system, developing guidelines for multi-sectional and inter-agency cooperation among nurses, nurses' support at outpatient settings.

3. Support for families with infants and children
Recently, custodial parents have faced many difficulties and challenges. To address this, we are conducting research on children's injury prevention and social environments for child-rearing parents.

4. Community health care for the elderly
We are conducting research on the health of the elderly to support favorable living conditions for this population. Our research includes (1) identification of service needs among frail elderly persons in community dwellings, (2) evaluation of community care services' impact on the elderly and their family caregivers, and (3) the development of an approach aimed at providing care for the terminally ill in community settings (e.g., monitoring of resident transfers).

5. Skills of public health nurses
Public health nurses use high-level support skills; however, many of these skills have not been identified through research. We aim to identify and standardize the skills of public health nurses, focusing in particular on skills regarding new community diagnostic method and group dynamics.

References

1. Yoshioka-Maeda K, Honda C, Iwasaki-Motegi R. Development of a Family-Friendly System for Japanese Parents Infected With COVID-19. Asia-Pacific journal of public health. 2021, 33(1) 145 - 146. doi: 10.1177/1010539520984361
2. Matsumoto H, Kageyama M, Yamamoto-Mitani N, Nagata S. The Use of a Public Space in a Public Housing Complex by Senior Citizens: A Qualitative Study. Journal of Aging and Environment 2021, 35(2), p.107-124.
3. Sumikawa Y, Yamamoto-Mitani N. Transitional care during COVID-19 pandemic in Japan: Calls for new strategies to integrate traditional approaches with information and communication technologies Bio Science Trends. 2021, 15(1), p.55-57. doi: 10.5582/bst.2021.01056.
4. Honda C, Naruse T, Yamana H, Yamamoto-Mitani N. Infant Injury Prevention Education for Pregnant Women Attending Antenatal Class: A Quasi-Experimental Study. International Journal of Environmental Reserch and Public Health. 2021, 18(18), 9393. doi.org/10.3390/ijerph18179393
5. Honda C, Sumikawa Y, Yoshioka□Maeda K, Iwasaki□Motegi R, Yamamoto□Mitani N. Confusions and responses of managerial public health nurses during the COVID-19 pandemic in Japan. Public health nursing. 2021,39,161-169. doi.org/10.1111/phn.13011
6. Sumikawa Y, Honda C, Yoshioka-Maeda K, Yamamoto-Mitani N. Characteristics of COVID-

19-related free telephone consultations by public health nurses in Japan: A retrospective study. Healthcare. 2021, 9(1022). doi.org/10.3390/healthcare9081022

7. Yoshioka-Maeda K, Sumikawa Y, Tanaka N, Honda C, Iwasaki-Motegi R, Yamamoto-Mitani N. Content Analysis of the Free COVID-19 Telephone Consultations Available during the First Wave of the Pandemic in Japan. Healthcare. 2021. 9(11), 1593. doi.org/10.3390/healthcare9111593
8. Naruse T, Yamamoto-Mitani N. Service Use Objectives among Older Adult Day Care Clients with Disability in Japan. Nursing reports. 2021, 11(3), 608-614. doi.org/10.3390/nursrep11030058.
9. Yamamoto-Takiguchi N, Naruse T, Fujisaki-Sueda-Sakai M, Yamamoto-Mitani N. Characteristics of Patient Safety Incident Occurrences Reported by Japanese Homecare Nurses: A Prospective Observational Study. Nurs Rep. 2021;11(4):997-1005. doi: 10.3390/nursrep11040090.
10. Matsumoto H, Maeda A, Igarashi A, Weller C, Yamamoto-Mitani N. Dementia education and training for the general public: a scoping review. Gerontology & Geriatrics Education. 2021. Nov (18), 1–31. doi.org/10.1080/02701960.2021.1999938.
11. Matsumoto H, Kawagoe M, Hotta S. Older Adults Used Fewer Home Care Services During The COVID-19 Pandemic: Findings From A Secondary Analysis Of An Urgent Survey In Japan. Annals of Geriatric Medicine and Research. 2021. 25(4), 286–93. doi.org/10.4235/agmr.21.0108.
12. 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. Progress in Community Health Partnerships: Research, Education, and Action. 2021 (in printing).
13. Sumino K, Iwasaki R, Naruse T, Yamamoto-Mitani N. The Background of Obtaining a Health Checkup among Middle-aged People in Rural Areas Who Have national health Insurance: A Qualitative Research (in Japanese). Jpn Health & Huan Ecology. 2020, 87(4), p161-172.

Health Sciences and Nursing

3. Clinical Nursing

Department of Gerontological Home Care and Long-term Care Nursing/Palliative Care Nursing

Professor

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Ayumi Igarashi, Ph.D., R.N.

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Introduction and Organization

The Department of Adult Health 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* has 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. Each student completes his/her Master's thesis or doctoral dissertation from developing research question from their own scientific interests regarding nursing practice for older people or adults in chronic stage.

In education, we emphasize critical thinking process as a researcher who conduct unique and original research: from cultivating perspectives as a researcher to come up with original research topic, developing research topic into unique research questions/ hypotheses, choosing appropriate research methods, and to developing valid research protocols.

Research

In research, we aim to contribute to the development of nursing science and improvement in quality of nursing practice through collaborative research with clinicians. Especially 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.

As research methods, along with conventional statistical methods, we often utilize qualitative methods to understand 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 live as high-quality lives as possible, even with diseases/disabilities; the paradigm of long-term care is different from that of acute care that typically aim 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 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 quality of long-term care, including home care nursing. We have been developing them as a part of 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 provider working at long-term care facilities and homecare nurse agencies are limited compared to that working at critical hospital.

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 long time, it has not had a standardized method. We aim to develop a protocol on conducting case study that contributes to develop nursing science.

3) Establishment of support system for older people in the integrated community care

In the Japanese aged society, it is an urgent problem to establish a local structure supporting the life of the elderly persons by the community. As one of the measures to solve the problem, the evaluation of the appropriateness of the public services in the community is necessary. We have been examining what combination of services the senior adults are using and what factors are related to that use. We also examine the outcomes affected by the combination of the used services.

In addition, in the integrated community care, the utilization of the local resources, including nongovernmental services, is demanded. We have discussed the possibility of utilizing convenience stores, which exist closely in local communities in Japan, as a hub of the elderly support. We have conducted action research to promote collaboration with the convenience stores in the elderly support in community.

4) End-of-life care decision making in community-dwelling older people

We conduct research about end-of-life care preference of community dwelling elderly people (including facility for the elderly). In the Asian region, Japan, Hong Kong, and South Korea, which are aging societies, need to promote advanced care planning, and has been designed institutional plan. By conducting collaborate research in the three countries, we attempt to clarify common issues in the Asian region and problems inherent to Japan and propose concrete policies that the administration should do. Hence, we aim to contribute to promotion of Advanced Care Planning considering cultural factor.

5) Supporting employed family caregivers

In the super-aged society, the number of family members who have two roles, working and providing care to their own parents, are increasing. Our department contribute to the development of a program for employed family caregivers to prevent leaving their job because of care giving for their parents with dementia and enhance their work-life balance.

6) Prevention of turnover among homecare nurses who support community dwelling persons

Homecare nursing is one of the services which are essential to support community-dwelling persons. We

have conducted a cohort study to examine the factors related to actual homecare nurse's turnover. Furthermore, we have developed and evaluated the case-based program to prevent homecare nurse' turnover.

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. Giannetta N, Dionisi S, Stievano A, Eltaybani S, Abdelgawad ME, Katigri MR, Azadboni TT, López Soto PJ, Morales-Cané I, Ali I, Urban J, Shrestha S, Christensen M, Voutilainen A, Vaajoki A, Hamdan K, Rubicini G, Rivera Pizarro JY, Liquori G, Cassar M, Trapani J, Rocco G, Orsi GB, Di Simone E, Di Muzio M. Comparison across 12 countries on knowledge, attitude, and behavior scores about medication errors in Intensive Care Units: an international study. Eur Rev Med Pharmacol Sci. 2021;25(23): 7223-7230.
2. Eltaybani S, Abdelhalim GE, Abdelgawad ME. Nursing students' and educators' experience with elearning during a pandemic: An online survey. Nurs Forum. 2021;56 (4) :878-888.
3. Eltaybani S, Ahmed FR. Family satisfaction in Egyptian adult intensive care units: A mixed-method study. Intensive Crit Care Nurs.2021;66: 103060.
4. Lepore M, Edvardsson D, Meyer J, Igarashi A. How long-term care quality assurance measures address dementia in Australia, England, Japan, and the United States. Aging and Health Research. 2021; 1(2):100013.
5. Yamamoto-Takiguchi N, Naruse T, Fujisaki-Sueda-Sakai M, Yamamoto-Mitani N.

Characteristics of Patient Safety Incident Occurrences Reported by Japanese Homecare Nurses: A Prospective Observational Study. Nurs Rep. 2021 Dec 14;11(4):997-1005.

6. Bowers BJ, Chu CH, Wu B, Thompson RA, Lepore MJ, Leung AYM, Brunkert T, Sharew NT, Yamamoto-Mitani N, Mateos JT, McGilton KS. What COVID-19 Innovations Can Teach Us About Improving Quality of Life in Long-Term Care. J Am Med Dir Assoc. 2021 May;22(5): 929-932.
7. Li CC, Yamamoto-Mitani N. Ward-level nurse turnover and related workplace factors in long-term care hospitals: A cross-sectional survey. J Nurs Manag. 2021 Sep;29(6):1587-1595.
8. Sumikawa Y, Yamamoto-Mitani N. Transitional care during COVID-19 pandemic in Japan: Calls for new strategies to integrate traditional approaches with information and communication technologies. Biosci Trends. 2021 Mar 15;15(1): 55-57.
9. Eltaybani S, Yamamoto-Mitani N, Ninomiya A, Igarashi A. The association between nurses' burnout and objective care quality indicators: a cross-sectional survey in long-term care wards. BMC Nurs. 2021 Feb23;20(1):34.
10. Fukui C, Igarashi A, Noguchi-Watanabe M, Sakka M, Naruse T, Kitamura S, Inagaki A, Takaoka M, Kobayashi H, Yasaka T, Yamamoto-Mitani N. Development of quality indicators for evaluating the quality of long-term care. Geriatr Gerontol Int. 2021 Apr;21(4):370-371.
11. Eltaybani S, Yasaka T, Fukui C, Inagaki A, Takaoka M, Suzuki H, Maruyama M, Yamamoto-Mitani N. Family-oriented interventions in long-term care residential settings: a scoping review protocol. JBI Evid Synth. 2021 Feb 9.
12. Sari DW, Noguchi-Watanabe M, Sasaki S, Sahar J, Yamamoto-Mitani N. Estimation of sodium and potassium intakes assessed by two 24-hour urine collections in a city of Indonesia. Br J Nutr. 2021 Nov 28;126(10):1537-1548.
13. Sakka M, Kita S, Sato I, Soejima T, Eguchi H, Tokita M, Yamamoto-Mitani N, Shimazu A, Kamibeppu K. Reliability and validity of the Japanese version of the Caregiving Interface Work Scale in employed Japanese family caregivers. Geriatr Gerontol Int. 2021 Feb;21(2): 254-261.
14. Eltaybani S, Igarashi A, Yamamoto-Mitani N. Palliative and end-of-life care education in

prelicensure nursing curricula: A nationwide survey in an Arab country. Nurse Educ Today. 2021 Jan;96:104644.
15. Kawakami A, Kwong EW, Lai CK, Song MS, Boo S, Yamamoto-Mitani N. Advance care planning and advance directive awareness among East Asian older adults:Japan, Hong Kong and South Korea. Geriatr Gerontol Int. 2021 Jan; 21(1):71-76.
16. Noguchi-Watanabe M, Yamamoto-Mitani N, Nagami Y, Eltaybani S, Inagaki A, Taniguchi Y. Homecare nurses' length of conversation and intention to remain at the workplace: A multilevel analysis. J Nurs Manag. 2021 May;29(4):721-730.

Department of Midwifery and Women's Health

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Introduction and Organization

The Department of Midwifery and Women's Health was established in 2002.
It has 4 faculty members introduced above, 23 graduate students (12 in master's courses, 11 in doctoral courses), and 10 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) Development of the strategy for safe delivery in El Salvador

      To reduce the maternal mortality ratio in El Salvador, a program for humanized childbirth based on scientific evidence that leads to maternal safety and comfort during childbirth is developed.
   5) 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.
   6) 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. International Committee of the Japan Society of Midwifery Education (2017 ~ 2018): Tharara-Sasagawa E, Ota Y, Matsuzaki M, Shimpuku Y, Oishi T. Visualization of midwifery education in 109 countries on a world map: Secondary analysis of the data from the International Confederation of Midwives(ICM). Journal of Japan Academy of Midwifery. 2021;35(1):48-56.
2. Kelleher, MM, Cro S, Cornelius V, Lodrup Carlsen KC, Skjerven HO, Rehbinder EM, Lowe AJ, Dissanayake E, Shimojo N, Yonezawa K, Ohya Y, Yamamoto-Hanada K, Morita K, Axon E, Surber C, Cork M, Cooke A, Tran L, Van Vogt E, Schmitt J, Weidinger S, McClanahan D, Simpson E, Duley L, Askie LM, Chalmers JR, Williams HC, Boyle RJ. Skin care interventions in infants for preventing eczema and food allergy. Cochrane Database of Systematic Reviews. 2021; Issue 2. Art. No.: CD013534. DOI: 10.1002/14651858.CD013534.pub2.
3. Kelleher MM, Cro S, Van Vogt E, Cornelius V, Lodrup Carlsen KC, Ove Skjerven H, Rehbinder EM, Lowe A, Dissanayake E, Shimojo N, Yonezawa K, Ohya Y, Yamamoto-Hanada K, Morita K, Cork M, Cooke A, Simpson EL, McClanahan D, Weidinger S, Schmitt J, Axon E, Tran L, Surber C, Askie LM, Duley L, Chalmers JR, Williams HC, Boyle RJ. Skincare interventions in infants for preventing eczema and food allergy: A cochrane systematic review and individual participant data meta-analysis. Clin Exp Allergy. 2021 doi: 10.1111/cea.13847.
4. Shimizu S, Yonezawa K, Haruna M, Sasagawa E, Hikita N, Minematsu T, Sanada H. Relationship between the skin barrier function of 2-week old infants after bathing and facial skin problems during the first 6 weeks of life: A prospective observational cohort study. Japan Journal of Nursing Science. 2021;28:e12408. doi: 10.1111/jjns.12408.
5. 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. Breastfeeding Medicine. 2021;Dec 21.
6. Murakami M, Yonezawa K, Shimizu S, Haruna M, Sasagawa E, Usui Y. Newborn-oriented and environmental factors for newborns' skin barrier functions. Japan Journal of Nursing Science. 2021;e12457.
7. Shiraishi M, Matsuzaki M, Tsunematsu R, Watanabe S, Kobayashi R, Haruna M. Effects of Individual Dietary Intervention on Nutrient Intake in Postpartum Japanese Women: A Randomized Controlled Trial. Nutrients. 2021; 13(9):3272.
8. Haruna M, Tanaka M, Nakano K, Nishihara N, Sasagawa E, Yonezawa K, Usui Y, Hikita N, Fujita M. A Cohort Study from Pregnancy to Postpartum during the COVID-19 Pandemic: J-PEACH Study. Developmental origins of health and disease research. 2021;10(1):46-48. (in Japanese)
9. Sasagawa E, Haruna M, Misago C. Humanization of childbirth in Latin America : Laws and regulations of midwifery care. Journal of Japan Academy of Midwifery, 2021;35(1):57-65. (in Japanese)
10. Sasagawa E, Haruna M, Misago C. Expansion and adoption of the concept of "humanization of childbirth" in the legislation and policies of Latin American countries. Journal of International Health. 2021;36(2):73-87. (in Japanese)
11. Yokoyama M, Oie C, Haruna M, Yonezawa K. The validation of predictive validity of infant 's skin assessment tool -Can it predict the onset of atopic dermatitis?- Study for Nursing Education. 2021;28:112-119. (in Japanese)

Department of Psychiatric Nursing

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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, a project research associate, part-time lecturers, visiting research fellows, 8 doctoral course students, 4 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. Chiba R, Yamazaki Y, Miyamoto Y, Funakoshi A. Related changes in personal recovery, benefit finding, and sense of coherence among people with chronic mental illness: a two-wave study. The Journal of Psychology. 2021. DOI: 10.1080/00223980.2021.1880360.
2. Kato Y, Chiba R, Yamaguchi S, Goto K, Umeda M, Miyamoto Y. Association between Work Environments and Stigma towards People with Schizophrenia among Mental Health Professionals in Japan. Healthcare. 2021; 9(2): 107. DOI: 10.3390/healthcare9020107.
3. Funakoshi A, Miyamoto Y. Relationships between medical incidents, clinical competency, and clinical experience in child and adolescent psychiatric in patient nursing: A structural equation modeling approach. J Child Adolesc Psychiatr Nurs. 2021. DOI: 10.1111/jcap.12333.
4. Iida, M, Watanabe, K, Imamura, K, Sakuraya, A, Asaoka, H, Sato, N, Nozawa, K, & Kawakami, N. Development and validation of the Japanese version of the team job crafting scale for nurses. Research in Nursing & Health 44.2, 2021: 329-343.
5. Iida, M, Sasaki, N, Kuroda, R, Tsuno, K, & Kawakami, N. Increased COVID-19-related workplace bullying during its outbreak: a 2-month prospective cohort study of full-time employees in Japan. Environmental and Occupational Health Practice, 2021.
6. Asaoka H, Sasaki N, Kuroda R, Tsuno K, Kawakami N. Workplace Bullying and Patient Aggression Related to COVID-19 and its Association with Psychological Distress among Health Care Professionals during the COVID-19 Pandemic in Japan. Tohoku J Exp Med. 2021; 255(4):283-289. DOI: 10.1620/tjem.255.283.
7. Asaoka H, Sasaki N, Imamura K, Kuroda R, Tsuno K, Kawakami N. Changes in COVID-19 measures in the workplace: 8-month follow-up in a cohort study of full-time employees in Japan. J Occup Health. 2021 Jan;63(1):e12273. DOI: 10.1002/1348-9585.12273.
8. Imamura K, Tran TTT, Nguyen HT, Sasaki N, Kuribayashi K, Sakuraya A, Bui TM, Nguyen

AQ, Nguyen QT, Nguyen NT, Nguyen KT, Nguyen GTH, Tran XTN, Truong TQ, Zhang MW, Minas H, Sekiya Y, Watanabe K, Tsutsumi A, Kawakami N. Effect of smartphone-based stress management programs on depression and anxiety of hospital nurses in Vietnam: a three-arm randomized controlled trial. Sci Rep. 2021 May 31; 11(1): 11353. DOI: 10.1038/s41598-021-90320-5. PMID: 34059737; PMCID: PMC8166974.

9. Sawada U, Shimazu A, Kawakami N, Miyamoto Y, Speigel L, Leiter MP. The Effects of the Civility, Respect, and Engagement in the Workplace (CREW) Program on Social Climate and Work Engagement in a Psychiatric Ward in Japan: A Pilot Study. Nursing Reports. 2021 Jun(2):320-30.
10. Yang CC, Watanabe K, Kawakami N. The Associations between Job Strain, Workplace PERMA Profiler, and Work Engagement. J Occup Environ Med. 2021 Dec 6. DOI: 10.1097/JOM.0000000000002455.
11. Watanabe K, Kawakami N. Association between sitting time at work and the onset of major depressive episode: a 1-year prospective cohort study using the Bayesian regression. BMC Public Health. 2021 Oct 29;21(1):1960. DOI: 10.1186/s12889-021-12059-y.
12. Orui M, Fukasawa M, Horikoshi N, Suzuki Y, Kawakami N. The ongoing activities of livelihood support counselors following nuclear disaster under the COVID-19 restrictions: A preliminary survey. Public Health Pract (Oxf). 2021 Nov;2:100107. DOI: 10.1016/j.puhip.2021.100107.
13. Kawakami N, Imamura K, Watanabe K, Sekiya Y, Sasaki N, Sato N; SMART-CBT Project Team. Effectiveness of an Internet-Based Machine-Guided Stress Management Program Based on Cognitive Behavioral Therapy for Improving Depression Among Workers: Protocol for a Randomized Controlled Trial. JMIR Res Protoc. 2021 Sep 29;10(9):e30305. DOI: 10.2196/30305.
14. Takano A, Fukasawa M, Watanabe K, Nishi D, Kawakami N. Adolescent Work Values and Drug Use in Adulthood: A Longitudinal Prospective Cohort Study. Subst Use Misuse. 2021;56(10): 1483-1492. DOI: 10.1080/10826084.2021.1936055.
15. Sato N, Watanabe K, Kawakami N. Mediating Effects of Work Eudemonic Well-being for the Association Between Psychosocial Work Environment and Overall Eudemonic Well-being Among Japanese Workers: A Cross-sectional Study. J Occup Environ Med. 2021 Aug 1;63(8): e542-e548. DOI: 10.1097/JOM.0000000000002276.
16. Sato N, Watanabe K, Nishi D, Kawakami N. Associations Between Personal Values and Work Engagement: A Cross-Sectional Study Using A Representative Community Sample. J Occup Environ Med. 2021 Jun 1;63(6):e335-e340. DOI: 10.1097/JOM.0000000000002209.
17. Yang CC, Lee KW, Watanabe K, Kawakami N. The association between shift work and possible obstructive sleep apnea: a systematic review and meta-analysis. Int Arch Occup Environ Health. 2021 Nov; 94(8): 1763-1772. DOI: 10.1007/s00420-021-01675-1.
18. Kawakami N, Sasaki N, Kuroda R, Tsuno K, Imamura K. The Effects of Downloading a Government-Issued COVID-19 Contact Tracing App on Psychological Distress During the Pandemic Among Employed Adults: Prospective Study. JMIR Ment Health. 2021 Jan 12;8(1): e23699. DOI: 10.2196/23699.
19. Sasaki N, Yasuma N, Obikane E, Narita Z, Sekiya J, Inagawa T, Nakajima A, Yamada Y, Yamazaki R, Matsunaga A, Saito T, Imamura K, Watanabe K, Kawakami N, Nishi D. Psycho-educational interventions focused on maternal or infant sleep for pregnant women to prevent the onset of antenatal and postnatal depression: A systematic review. Neuropsychopharmacol Rep. 41(1):2-13, 2021
20. Yasuma N, Imamura K, Watanabe K, Nishi D, Kawakami N, Takano A. Association between energy drink consumption and substance use in adolescence: A systematic review of prospective cohort studies. Drug Alcohol Depend. 219: 108470, 2021
21. Sasaki N, Imamura K, Nishi D, Watanabe K, Sekiya Y, Tsuno K, Kobayashi Y, Kawakami N. Internet-based acceptance and commitment

therapy programme 'Happiness Mom' for well-being: a protocol for a randomised controlled trial. BMJ Open. 26;11(2): e042167, 2021

22. Sasaki N, Obikane E, Vedanthan R, Imamura K, Cuijpers P, Shimazu T, Kamada M, Kawakami N, Nishi D. Development and Validation of Implementation Outcome Scales for Digital Mental Health (iOSDMH). JMIR Formative Research 23;5(11):e24332, 2021
23. Asaoka H, Koido Y, Kawashima Y, Ikeda M, Miyamoto Y, Nishi D. Longitudinal change in depressive symptoms among healthcare professionals with and without COVID-19 vaccine hesitancy from October 2020 to June 2021 in Japan. Industrial Health (Epub ahead of print)
24. Sasaki N, Akiyama H, Kawakami N, Nishi D. Preconception menstrual cycle disorder and antenatal depression: A cross-sectional study with pre-recorded information. J Psychosom Obstet Gynaecol. (Epub ahead of print)
25. Asaoka H, Koido Y, Kawashima Y, Ikeda M, Miyamoto Y, Nishi D. Longitudinal Change of Psychological Distress among Healthcare Professionals with and without Psychological First Aid Training Experience during the COVID-19 Pandemic. International Journal of Environmental Research and Public Health. 18(23):12474, 2021
26. Hidaka Y, Sasaki N, Imamura K, Tsuno K, Kuroda R, Kawakami N. Changes in fears and worries related to COVID-19 during the pandemic among current employees in Japan: a 5-month longitudinal study. Public health. 2021 Sep 1;198:69-74.
27. Hidaka Y, Watanabe K, Imamura K, Tatha O, Kawakami N. Reliability and validity of the Chinese version of the New Brief Job Stress Questionnaire (New BJSQ) among workers in China. Industrial health. 2021 Nov 1.
28. Komase Y, Watanabe K, Hori D, Nozawa K, Hidaka Y, Iida M, Imamura K, Kawakami N. Effects of gratitude intervention on mental health and well-being among workers: A systematic review. Journal of Occupational Health, 2021;63: e12290. DOI: 10.1002/1348-9585.12290.
29. Komase Y, Watanabe K, Natsu S, Kawakami N. The effect of perceived gratitude from others on work engagement: a cross-sectional study. Journal of Occupational and Environmental Medicine. 2021; 63: e592-e595. DOI: 10.1097/JOM.0000000000002294.
30. Komase Y, Watanabe K & Kawakami N. Effects of a gratitude intervention program on work engagement among Japanese workers: a protocol for a cluster randomized controlled trial. BMC Psychol 9, 35 (2021). DOI: 10.1186/s40359-021-00541-6.

Department of Gerontological Nursing / Wound Care Management

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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.

Especially noteworthy, the Department of Advanced Nursing Technology, which was established in December 2012, works as a social cooperation program to promote team nursing intervention and research involving the clinical division, the nursing department at the University of Tokyo Hospital, and the Division of Health Sciences and Nursing at the Graduate School of Medicine. Through this program, nurses can scientifically study the subject of nursing, including research in epidemiological surveys and molecular- and gene-level topics. Furthermore, the technology and medical equipment developed by companies can be evaluated in the hospital, offering new nursing technologies suitable for needs in clinical sites.

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 has been the director, and faculty staff members in our department have been involved in the Division of Care Innovation in GNRC as a concurrent position.

Gerontological Nursing and Wound Care Management is currently headed by one professor and assisted by an associate professor, two research

associates, a project research associate, a project academic specialist, an assistant clerk, five part-time lecturers for undergraduate courses, and seven part-time lecturers for graduate courses. The student body consists of six doctoral course students and six 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 2021, we conducted an 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 pharmaceutics required for nursing practice. The main content themes in the 2021 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 pharmaceutics

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 2021 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 2021 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, feeding and swallowing difficulty, 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) Nursing Science and Engineering (S2 in 4th yr; 2 credits)

Gaining a thorough understanding of a given medical situation, as well as determining the appropriate medical intervention for a patient require the knowledge and skills from Nursing Science and Engineering. These include the processes involved in translational research: clinical observation, exploration of the mechanisms underlying the patient's symptoms, development of objective measurement methods, and the development of devices and systems for intervention and the clinical evaluation. This series of lectures is to learn about cutting-edge research, and to understand the linkage between research and clinical activities. In 2021, lectures and exercises were given on the necessity and significance of nursing science and engineering, research methods in nursing science and engineering, and their applications.

6) 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 2021, 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), and remote observation of actual geriatric nursing care.

2. Graduate course

1) Gerontological Nursing I (S1; 2 credits)

The main theme of Gerontological Nursing I in 2021 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 2021 were as follows:

a) Physiological activity and deficiency of micronutrients - with a focus on zinc - and nutritional management of pressure injuries with complications
b) Gerontological nursing: dysphagia
c) Nutrition management in elderly nursing
d) Diabetic foot ulcer management initiatives: an attempt at globalization
e) The meeting of research, clinical practice, and education: Kindness is not merely for the sake of patients
f) Prevention of pressure injury recurrence in the elderly
g) Effects of obesity on skin
h) End-of-Life care for the elderly: creating a prosperous last years

3) Wound Care Management I (S2; 2 credits)

The main purpose of Wound Care Management I in 2021 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) Structure and function of the skin; wound healing
b) Prediction and prevention of wounds
c) Basics of pressure injury, nursing efforts regarding wound care
d) Assessment of wounds
e) Treatment and care of wounds
f) Institutions and policies related to wound care and management

4) Wound Care Management II (A2; 2 credits)

The main theme of Wound Care Management II in 2021 was to obtain deeper insight in our own research knowledge through lectures and discussion by specialists from various basic and advanced research fields in the Division of Care Innovation in GNRC.

5) Master's theses

The following research themes were submitted in 2021:

- "An expert knowledge algorithm and model predicting wound healing trends for a decision support system for pressure injury management in home care nursing"
- "Development of biomarkers in first-void urine samples for urinary tract infection assessment"
- "Expression of NPPB, ITGB6, CPNE4, EML5, and ITSN1 in exudates of infected full-thickness wounds in rats and of critically colonized pressure injuries of patients"

6) Doctoral theses

The following research themes were submitted in 2021:

- "Investigation of the role of dysbiotic wound microbiota on the establishment of critical colonization"
- "Development of a method to distinctly identify persistent and blanchable redness by skin blotting in mice"
- "Integration of nurse call log data and electronic medical record records and development of a fall risk assessment method using the integrated database" (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.

In July 2021, Professor Sanada chaired the 30th Annual Meeting of the Japanese Society for Wound, Ostomy and Continence Management and the 9th Asia Pacific Enterostomal Therapy Nurse Association Conference (APETNA) (held simultaneously). With the aim of advancing academic development and improving the quality of clinical practice in the field of wound, ostomy, and incontinence management in the Asia-Pacific region, she organized the conference under the theme "Integrating Science and Art for Next Generation WOC Management," which was held online and on-demand. Integrating Science and Art for Next-Generation WOC Management. More than 2,600 participants in total attended the conference, which was very well received both domestically and internationally.

In September 2021, we organized the 8th introductory seminar for bioengineering nursing research as a webinar. In this webinar, a new research framework "Bioengineering Nursing," consisting of nursing biology (which investigates, in detail, the mechanisms of a target phenomenon), nursing engineering (which develops technologies for the clarified target), and nursing translational research (which evaluates the technologies in the clinical field and further explores new clinical problems) was introduced to many nursing researchers and clinical nurses. This seminar is held annually since 2013. In 2021, the seminar was held for four days with a total of 1,983 participants.

Professor Sanada was retiring at the end of FY2021 and held her final lecture, "Nursing Care Innovation," in a hybrid format at the University of Tokyo's Yasuda Auditorium in March 2022. The number of on-site participants exceeded 280 at the venue and 850 online. It was an opportunity to convey to the next generation her achievements over the years and the suggestions she has gained from them, as well as to express her gratitude to the many people she has connected with through her educational and research activities. In addition, the WUWHS Lifetime Achievement Award was presented by the World Union of Wound Healing Societies, a federation of wound healing-related societies from around the world, in recognition of her many years of contributions to the field of wound healing.

Regarding international activities, our department

has been promoting collaborative research with researchers in universities around the world. Our counterparts include University of California, Los Angeles (USA), Florida University (USA), Curtin University (Australia), Nottingham Trent University (UK) and Universitas Muhammadiyah Pontianak. Professor Sanada has been working as a member in both the Continental Board for World Union of Wound Healing Societies and the International Board of Directors for International Lymphoedema Framework.

2. Research fields and themes in 2021

1) Basic experimental studies:

・Development of a novel method for controlling wound infection focusing on gene expression of bacteria and hosts
・Evaluation of wound condition using exudates
・Skin blotting for analyzing physiological status of the skin
・Development of a new technique for detecting wound biofilm
・Cutaneous wound healing and diabetes mellitus
・Research on scalp care science

2) Nursing engineering:

・Development of a new air mattress equipped with interface pressure-sensing system and automatic pressure control
・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
・Development of a new peripheral intravenous catheter for catheter failure prevention

3) Clinical studies:

・Novel assessment technologies for pressure injuries
・Establishment of methods for predicting skin tear development
・Establishment of a novel diagnosis method for silent aspiration
・Establishment of a novel assessment method for constipation using ultrasonography
・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, as follows:

・2021 the Japanese Society for Wound, Ostomy, and Continence Management Academic Paper Excellence Award (July, 2021)
Kunimitsu M, Nakagami G, Kitamura A, Minematsu T, Ogai K, Sugama J, Takada C, Sanada H. Temporal changes in the diversity and composition of the bed microbiota of patients with pressure ulcers.
・10th International Lymphedema Framework Japan Research Council Best Paper Award (September, 2021)
Dai M, Shogenji M, Matsui K, Kimori K, Sato A, Maeba H, Okuwa M, Konya C, Sugama J, Sanada H. Validity of pocket ultrasound device to measure thickness of subcutaneous tissue for improving upper limb lymphoedema assessment.
・IEEE EMBS East and Central Japan Chapter/West Japan Chapter Young Researcher Award (November, 2021)
Noyori S, Nakagami G, Noguchi H, Mori T, Sanada H. A Small 8-Electrode Electrical Impedance Measurement Device for Urine Volume Estimation in the Bladder. EMBC, 2021
・51st Japan Society for Wound Healing Research Award (November, 2021)
Koudounas S, Minematsu T, Mugita Y, Nakagami G, Sanada H. Development of a rat model for incontinence-associated dermatitis in patients with urinary infection.
・The 20th Japan Academy of Nursing Science Academic Paper Award for Excellence (December, 2021)
Yoshida M, Kagaya H, Kamakura Y, Miura Y, Saitoh E, Okawa Y, Sanada H. Safety and the

effectiveness of a new education program for nurses to assess swallowing function using fiberoptic endoscopic evaluation of swallowing (FEES).

- The 20th Japan Academy of Nursing Science Academic Paper Excellent Award (December, 2021)
  Matsumoto M, Tsutaoka T, Nakagami G, Tanaka S, Yoshida M, Miura Y, Sugama J, Okada S, Ohta H, Sanada H. Deep learning-based classification of rectal fecal retention and analysis of fecal properties using ultrasound images in older adult patients.
- The 20th Japan Academy of Nursing Science Academic Paper Incentive Award (December, 2021)
  Abe-Doi M, Murayama R, Komiyama C, Sanada H. Incidence, risk factors, and assessment of induration by ultrasonography after chemotherapy administration through a peripheral intravenous catheter.
- WUWHS Lifetime Achievement Award Awards (March, 2022)
  Sanada H

References

1. Astrada A, Nakagami G, Minematsu T, Goto T, Kitamura A, Mugita Y, Sanada H. Concurrent validity of biofilm detection by wound blotting on chronic wounds. J Wound Care. 2021;30(Sup4): S4-S13.
2. Miura Y, Tamai N, Kitamura A, Yoshida M, Takahashi T, Mugita Y, Tobita I, Arita M, Urai T, Dai M, Noguchi H, Matsumoto M, Mukai K, Nakagami G, Ota E, Sugama J, Sanada H. Diagnostic accuracy of ultrasound examination in detecting aspiration and pharyngeal residue in patients with dysphagia: A systematic review and meta-analysis. Jpn J Nurs Sci. 2021;18:e12396.
3. Sari WD, Minematsu T, Yoshida M, Noguchi-Watanabe M, Tomida S, Kitamura A, Abe M, Sanada H. Validity of skin blot examination for albumin and nerve growth factor β to detect itching of the skin in Indonesian older adults. J Tissue Viability. 2021;30(1):42-50.
4. Tamai N, Minematsu T, Sanada H. Changes in scalp epidermal thickness using in vivo reflectance confocal microscopy in breast cancer patients undergoing chemotherapy: a case series. J Nurs Sci Eng. 2021;8:143-50.
5. Shibata K, Ogai K, Ogura K, Urai T, Aoki M, Arisnandi D, Takahashi N, Okamoto S, Sanada H, Sugama J. Skin physiology and its microbiome as factors associated with the recurrence of pressure injuries. Biol Res Nurs. 2021;23(1):75-81.
6. Nagata T, Noyori S, Noguchi H, Nakagami G, Kitamura A, Sanada H. Skin tear classification using machine learning from digital RGB image. J Tissue Viability. 2021;30(4):588-93.
7. Koudounas S, Mugita Y, Minematsu T, Nakagami G, Weller C, Sanada H. Does the presence of bacterial urinary infection contribute to the development of incontinence-associated dermatitis? A scoping review. J Tissue Viability. 2021;30(2): 256-61.
8. Takahashi T, Shintani Y, Murayama R, Noguchi H, Abe-Doi M, Koudounas S, Nakagami G, Mori T, Sanada H. Ultrasonographic measurement of blood flow of peripheral vein in the upper limb of healthy participants: a pilot study. J Jpn WOCM. 2021;25(3).
9. Minematsu T, Dai M, Tamai N, Nakagami G, Urai T, Nakai A, Nitta S, Kataoka Y, Kuang W, Kunimitsu M, Tsukatani T, Oyama H, Yoshikawa T, Takada C, Kuwata M, Sanada H. Risk scoring tool for forearm skin tears in Japanese older adults: A prospective cohort study. J Tissue Viability. 2021;30(2):155-60.
10. Noguchi H, Miyahara M, Takahashi T, Sanada H, Mori T. Modeling for change of daily nurse calls after surgery in an orthopedics ward using bayesian statistics. Comput Inform Nurs. 2021; 39(7):375-83.
11. Murayama R, Abe-Doi M, Kogure T, Takahashi T, Kanno C, Ishigaki M, Sanada H. The influence of peripheral intravenous catheterization on the sleep quality of ophthalmic inpatients: An observational study. J Nurs Sci Eng. 2021;8:134-42.
12. Shimizu S, Yonezawa K, Haruna M, Sasagawa E, Hikita N, Sanada H, Minematsu T. Relationship between the skin barrier function of 2-week old infants after bathing and facial skin problems during the first 6 weeks of life: A prospective observational cohort study. Jpn J Nurs Sci. 2021: e12408.

13. Tsukatani T, Minematsu T, Dai M, Tamai N, Nakagami G, Sugama J, Takada C, Sanada H. Polymorphism analysis of candidate risk genes for pressure injuries in older Japanese patients: A cross-sectional study at a long-term care hospital. Wound Repair Regen. 2021;29(5):741-51.
14. 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. Int J Nurs Stud. 2021;119:103932.
15. Matsumoto M, Tamai N, Miura Y, Okawa Y, Yoshida M, Igawa Y, Nakagami G, Sanada H. Evaluation of a point-of-care ultrasound education program for nurse educators. J Contin Educ Nurs. 2021;52(8):375-81.
16. Qin Q, Oe M, Ohashi Y, Shimojima Y, Imafuku M, Dai M, Nakagami G, Yamauchi T, Yeo S, Sanada H. Factors associated with the local increase of skin temperature, 'hotspot,' of callus in diabetic foot: A cross-sectional study. J Diabetes Sci Technol. 2021;19322968211011181.
17. Dai M, Minematsu T, Ogawa Y, Takanishi Y, Sugama J, Sanada H. Subjective thermal sensation effect of cool feeling compression stocking for patients with lower limb Lymphedema: A preliminary pre-post study. J Jpn WOCM. 2021; 25(1):10-7.
18. Mugita Y, Minematsu T, Nakagami G, Sanada H. Promoting effect of acylated homoserine lactone on the healing of tissue damage in incontinence-associated dermatitis model rats. J Wound Care. 2021;30(Sup9a):XIi-XIxi.
19. Abe-Doi M, Murayama R, Komiyama C, Tateishi R, Sanada H. Effectiveness of ultrasonography for peripheral catheter insertion and catheter failure prevention in visible and palpable veins. J Vasc Access. 2021;11297298211022078.
20. 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. Jpn J Nurs Sci. 2021; 18(4):e12436.
21. Kunimitsu M, Kataoka Y, Nakagami G, Weller DC, Sanada H. Factors related to the composition and diversity of wound microbiota investigated using culture-independent molecular methods: a scoping review. Drug Discov Ther. 2021;15(2):78-86.
22. Hsu WJ, Minematsu T, Nakagami G, Koudounas S, Tomida S, Nakai A, Kunimitsu M, Nitta S, Sanada H. Identification of microRNAs responsive to shear loading in rat skin. Int Wound J. 2021;19(2):351-61.
23. Dai M, Minemasu T, Ogawa Y, Nakagami G, Sanada H. Association of dermal hypoechogenicity and a history of cellulitis in lower extremity lymphedema patients: A cross-sectional observational study. Lymphat Res Biol. 2021. https://doi.org/10.1089/lrb.2021.0004
24. Kunimitsu M, Nakagami G, Kitamura A, Minematsu T, Mugita Y, Ogai K, Sugama J, Aoki M, Takada C, Sanada H. Dissemination of microbiota between wounds and the beds of patients with pressure injuries: A cross-sectional study. Wound Pract Res. 2021;29(2):70-6.
25. Mugita Y, Koudounas S, Nakagami G, Weller C, Sanada H. Assessing absorbent products' effectiveness for the prevention and management of incontinence-associated dermatitis caused by urinary, faecal or double adult incontinence: a systematic review. J Tissue Viability. 2021;30(4): 599-607.
26. Yoshinaga N, Nakagami G, Fukahori H, Shimpuku Y, Sanada H, Sugama J. Initial impact of the covid-19 pandemic on time Japanese nursing faculty devote to research: cross-sectional survey. Jpn J Nurs Sci. 2021;19(1):e12454.
27. Dai M, Nakagami G, Sato A, Koyanagi H, Kohta M, Moffatt C, Murray S, Franks P, Sanada H, Sugama J. Association between access to specialists and history of cellulitis among patients with lymphedema: secondary analysis using the National LIMPRINT Database. Lymphat Res Biol 2021;19(5):442-6.
28. Matsumoto M, Karube M, Nakagami G, Kitamura A, Tamai N, Miura Y, Kawamoto A, Kurita M, Miyake T, Hayashi C, Kawasaki A, Sanada H. Development of an automatic

ultrasound image classification system for pressure injury based on deep learning. Appl Sci. 2021; 11(17):7817.
29. Haba D, Nakagami G, Minematsu T, Sanada H. Low-frequency vibration promotes AMPK-mediated glucose uptake in 3T3-L1 adipocytes. Heliyon. 2021;7(9):e07897.
30. 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. J Nurs Sci Eng. 2021;8:220-9.
31. Hasegawa Y, Yoshida M, Sato A, Fujimoto Y, Minematsu T, Sugama J, Sanada H. A change in temporal muscle thickness is correlated with past energy adequacy in bedridden older adults: A prospective cohort study. BMC Geriatr. 2021; 21(1):182.
32. Yamane T, Nakagami G, Sanada H, Oishi Y. Hydrocellular foam dressing regulates MMP1a, MMP9, MMP10, MMP12 and MMP13 gene expression in periwound skin. Jpn J PU. 2021; 23(4):313-7.
33. Takahashi T, Murayama R, Abe-Doi M, Miyahara M, Kanno C, Nakagami G, Sanada H. Catheter failure in the administration of hyperosmotic drugs through a peripheral vein and vascular selection: A retrospective cohort study. Drug Discov Ther. 2021;15(5):236-40.
34. Maeda T, Tamai N, Minematsu T, Noguchi H, Yabunaka K, Nakagami G, Neya M, Sanada H. The relationship between pressure injuries and dynamic buttock pressure distributions during performance in wheelchair basketball athletes. Wound Pract Res. 2021;29(4): 211-8.
35. Fujisawa C, Hamanoue M, Kawano Y, Murata D, Akishima-Fukasawa Y, Okaneya T, Minematsu T, Sanada H, Tsuburaya K, Isshiki T, Mikami T, Hanawa T, Akasaka Y. The role for miRNA146b-5p in the attenuation of fibrosis and angiogenesis by targeting PDGFRα in skin wounds. J Invest Dermatol. 2021;S0022-202X(21)02619-1.
36. Kitamura A, Nakagami G, Matsumoto M, Hayashi C, Kawasaki A, Sanada H. Effectiveness of a robotic mattress with automatic inner-air cell adjustment and continuous pressure mapping on prevention of pressure ulcer deterioration in a critically ill patient with a pressure ulcer in the sacrum. J Jpn WOCM. 2021;25(4):689-96.
37. Kitamura A, Nakagami G, Minematsu T, Kunimitsu M, Sanada H. Establishment of an infected wound model by bacterial inoculation on wound surface in rats. J Nurs Sci Eng. 2021;9:1-8.
38. 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. Jpn J PU. 2021; 24(1):14-28.
39. Higashimura S, Tamai N, Nakagami G, Tobe H, Sanada H. A pilot epidemiological study on chronic dehydration of older adults in home care setting. J Nurs Sci Eng. 2022;9:123-35.
40. Matsumoto M, Misawa N, Tsuda M, Manabe N, Kessoku T, Tamai N, Kawamoto A, Sugama J, Tanaka H, Kato M, 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.
41. 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; 25(3):576-84.
42. 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. Int J Older People Nur. 2022;e12458.
43. 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. J Vasc Acces. 2022; 11297298221075169.

44. 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. Jpn J Nurs Sci. 2022;e12484.
45. Noyori S, Nakagami G, Sanada H. Non-invasive urine volume estimation in the bladder by electrical impedance-based methods: A review. Med Eng Phys. 2021;101:103748.
46. Abe-Doi M, Oe M, Ikeda M, Murayama R, Komiyama C, Sanada H. Factors affecting blood glucose self-monitoring skill acquisition: Nursing interventions for elderly individuals with diabetes (in Japanese). Jpn J Nurs Sci. 2021;8:122-33.
47. Mitsuhashi Y, Murayama R, Mahira T, Uchida M, Oe M, Sanada H, Komiyama C. Effect of using a peripheral intravenous catheter with a backflow prevention valve on the operator's fear level and venipuncture success (in Japanese). Jpn J Nurs Sci. 2021;8:77-85.
48. Kitamura A, Nakagami G, Watanabe C, Aoki K, Inada H, Konya C, Taniguchi T, Yoshida M, Tansaka H, Sanada H. Efficacy of teleconsultations with Wound, Ostomy and Continence Nurses for patients with pressure ulcers in the community setting (in Japanese). J Jpn WOCM. 2021;25(3): 654-60.
49. Matsumoto M, Ishibashi K, Kitamura A, Tamai N, Miura Y, Takahashi T, Higashimura S, Nakagami G, Sanada H. Development of AI-based fecal retention assessment method for rectal ultrasonography videos taken by home-visit nurses (in Japanese). Jpn J Nurs Sci. 2021;9:34-46.

International Health

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Introduction and Organization

As of March 2022 the department, headed by Professor Masahiro Hashizume, included the following staff complement; one associate professor (Chris Fook Sheng Ng); three project assistant professors (Shuhei Nomura, Ashraful Alam and Paul Lester Chua); 2 post-doctoral fellows; 10 adjunct lecturers; 12 doctoral students; and 5 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, interdisciplinary 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 2020:

- Introduction to demographic analysis
- Sustainable Development Goals: global policy and health agenda
- Overview of the global burden of disease
- Global environmental change and health
- Global health governance
- Population ageing and its implications for health systems
- Health system and innovation
- Innovations in maternal and child health
- Infectious disease surveillance system
- Economic evaluation and cost-effective analysis
- Cancer epidemiology and prevention
- Comparative risk assessment
- Air pollution and health
- Universal health coverage
- Planetary health
- Equity in health and social inclusion

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.

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. Vicedo-Cabrera AM, Tobias A, Jaakkola JJK, Honda Y, Hashizume M, Guo Y, Schwartz J, Zanobetti A, Bell ML, Armstrong B, Katsouyanni K, Haines A, Ebi KL, Gasparrini A. Global mortality burden attributable to non-optimal temperatures. *Lancet.* 2022;399(10330):1113.
2. Chua PLC, Ng CFS, Tobias A, Seposo XT, Hashizume M. Associations between ambient temperature and enteric infections by pathogen: a systematic review and meta-analysis. *Lancet Planet Health.* 2022;6(3):e202-e218.
3. Chua PLC, Huber V, Ng CFS, Seposo XT, Madaniyazi L, Hales S, Woodward A, Hashizume M. Global projections of temperature-attributable mortality due to enteric infections: a modelling study. *Lancet Planet Health.* 2021;5(7):e436-e445.

4. Chua PLC, Ng CFS, Madaniyazi L, Seposo X, Salazar MA, Huber V, Hashizume M. Projecting Temperature-Attributable Mortality and Hospital Admissions due to Enteric Infections in the Philippines. *Environ Health Perspect.* 2022; 130(2):27011.
5. Onozuka D, Tanoue Y, Nomura S, Kawashima T, Yoneoka D, Eguchi A, Ng CFS, Matsuura K, Shi S, Makiyama K, Uryu S, Kawamura Y, Takayanagi S, Gilmour S, Hayashi TI, Miyata H, Sera F, Sunagawa T, Takahashi T, Tsuchihashi Y, Kobayashi Y, Arima Y, Kanou K, Suzuki M, Hashizume M. Reduced mortality during the COVID-19 outbreak in Japan, 2020: a two-stage interrupted time-series design. *Int J Epidemiol.* 2022;51(1):75-84.
6. Sera F, Armstrong B, Abbott S, Meakin S, O'Reilly K, von Borries R, Schneider R, Royé D, Hashizume M, Pascal M, Tobias A, Vicedo-Cabrera AM; MCC Collaborative Research Network; CMMID COVID-19 Working Group, Gasparrini A, Lowe R. A cross-sectional analysis of meteorological factors and SARS-CoV-2 transmission in 409 cities across 26 countries. *Nat Commun.* 2021;12(1):5968.
7. Madaniyazi L, Armstrong B, Chung Y, Ng CFS, Seposo X, Kim Y, Tobias A, Guo Y, Sera F, Honda Y, Gasparrini A, Hashizume M: Multi-country Multi-city (MCC) Collaborative Research Network. Seasonal variation in mortality and the role of temperature: a multi-country multi-city study. *Int J Epidemiol.* 2021;51(1):122-133.
8. Vicedo-Cabrera AM, Scovronick N, Sera F, Royé D, Schneider R, Tobias A, Astrom C, Guo Y, Honda Y, Hondula DM, Abrutzky R, Tong S, de Sousa Zanotti Stagliorio Coelho M, Saldiva PHN, Lavigne E, Correa PM, Ortega NV, Kan H, Osorio S, Kyselý J, Urban A, Orru H, Indermitte E, Jaakkola JJK, Ryti N, Pascal M, Schneider A, Katsouyanni K, Samoli E, Mayvaneh F, Entezari A, Goodman P, Zeka A, Michelozzi P, de'Donato F, Hashizume M, Alahmad B, Diaz MH, De La Cruz Valencia C, Overcenco A, Houthuijs D, Ameling C, Rao S, Ruscio FD, Carrasco-Escobar G, Seposo X, Silva S, Madureira J, Holobaca IH, Fratianni S, Acquaotta F, Kim H, Lee W, Iniguez C, Forsberg B, Ragettli MS, Guo YLL, Chen BY, Li S, Armstrong B, Aleman A, Zanobetti A, Schwartz J, Dang TN, Dung DV, Gillett N, Haines A, Mengel M, Huber V, Gasparrini A. The burden of heat-related mortality attributable to recent human-induced climate change. *Nat Clim Chang.* 2021;11(6):492-500.

Department of Community and Global Health

Professor, Academic Leader

Masamine Jimba, MD, PhD, MPH

Lecturer

Akira Shibanuma, PhD

Assistant Professors

Junko Kiriya, PhD, Ken Ing Cherng Ong, PhD

Project Assistant Professors

Rogie Royce Carandang, RPh, MPH, MSc, PhD, Jennifer Lisa Sakamoto, MSc

Website: http://www.ich.m.u-tokyo.ac.jp/en/index.html

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-present).

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 developing 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 2022, the members of the department include the department chair and professor, 1 lecturer, 2 assistant professors, 2 project assistant professors, 3 secretaries, 12 visiting lecturers, 17 doctoral students, 18 master's degree students, and 43 visiting scientists. More than half of the students in this department are international students.

International Cooperation Activities

As part of our international cooperation activities, we provided technical assistance of developing the maternal and child health handbook in Russia. As Regional Vice-President for Northern Part of Western Pacific of International Union for Health Promotion and Education, Professor Jimba contributed to enhancing health promotion at the global and regional level. Moreover, as the Immediate–Past President of Asia-Pacific Academic Consortium for Public Health, Professor Jimba took a leading role in improving public health research and practices in the region.

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. Health-seeking behaviours in a malaria endemic district in Lao People's Democratic Republic: a mixed methods study. Ong KIC, Khattignavong P, Keomalaphet S, Iwagami M, Brey P, Kano S, Jimba M. BMJ Open. 2021 Dec 13;11(12): e055350.
2. Obituaries: Susumu Wakai. Jimba M. BMJ. 2021; 375:n2701
3. Multilevel factors influencing contraceptive use and childbearing among adolescent girls in Bara district of Nepal: a qualitative study using the socioecological model. Sekine K, Khadka N, Carandang RR, Ong KIC, Tamang A, Jimba M. BMJ Open. 2021 Oct 19;11(10):e046156.
4. Positive deviance for promoting dual-method contraceptive use among women in Uganda: a cluster randomised controlled trial. Kosugi H, Shibanuma A, Kiriya J, Ong KIC, Mucunguzi S, Muzoora C, Jimba M. BMJ Open. 2021 Aug 18;11(8):e046536.
5. Community-based model for the delivery of antiretroviral therapy in Cambodia: a quasi-experimental study protocol. Tuot S, Teo AKJ, Prem K, Chhoun P, Pall C, Ung M, Ly PS, Jimba M, Yi S. BMC Infect Dis. 2021 Aug 6;21(1):763.
6. 壁に耳あり、耳に壁あり（？）. 神馬 征峰. 国際保健医療. 2021;36(2):91-94.
7. ［追悼　若井　晋先生］ 若井晋：次世代へのメッセージ. 神馬 征峰. 国際保健医療. 2021; 36(2):25-34.
8. Roles of the Maternal and Child Health Handbook and Other Home-Based Records on Newborn and Child Health: A Systematic Review.

Carandang RR, Sakamoto JL, Kunieda MK, Shibanuma A, Yarotskaya E, Basargina M, Jimba M. Int J Environ Res Public Health. 2021 Jul 13;18(14):7463.

9. Evaluation of a package of continuum of care interventions for improved maternal, newborn, and child health outcomes and service coverage in Ghana: A cluster-randomized trial. Shibanuma A, Ansah EK, Kikuchi K, Yeji F, Okawa S, Tawiah C, Nanishi K, Addei S, Williams J, Asante KP, Oduro A, Owusu-Agyei S, Gyapong M, Asare GQ, Yasuoka J, Hodgson A, Jimba M; Ghana EMBRACE Implementation Research Project Team. PLoS Med. 2021 Jun 25;18(6): e1003663.
10. Evaluating Local Multilingual Health Care Information Environments on the Internet: A Pilot Study. Miller R, Doria-Anderson N, Shibanuma A, Sakamoto JL, Yumino A, Jimba M. Int J Environ Res Public Health. 2021 Jun 25; 18(13):6836.
11. Difference in factors associated with continuum of care completion rate from pregnancy to postpartum period in rural Nepal: a community-based, cross-sectional study. Silwal RC, Shibanuma A, Poudyal AK, Ikeda S, Jimba M. BMJ Open. 2021 Jun 16;11(6):e044928.
12. Community Theater for Health Promotion in Japan. In Arts and Health Promotion: Tools and Bridges for Practice, Research, and Social Transformation. Sandhu H, Hirose N, Yui K, Jimba M. Springer: Cham, Switzerland; 2021. p. 103-119.
13. DISASTERSHOCK How Schools Can Cope with the Emotional Stress of a Major Disaster: A Manual for Principals and Teachers. Gerrard B, Buchanan K, Buchanan T, De Young A, Giampaoli J, Giraudo S, Jimba M, Toren NK, Kenardy J, Korzeniowski C. Institute for School-Based Family Counseling: Oxford, United Kingdom; 2021.
14. Factors associated with the length of stay at health facilities after childbirth among mothers and newborns in Dhading, Nepal: a cross-sectional study. Ikeda S, Shibanuma A, Silwal R, Jimba M. BMJ Open. 2021 May 4;11(5):e042058.
15. Understanding frailty among older people living in old age homes and the community in Nepal: A cross-sectional study. Shah R, Carandang RR, Shibanuma A, Ong KIC, Kiriya J, Jimba M. PLoS One. 2021 Apr 29;16(4):e0251016.
16. Identifying the causal effect of child marriage on unmet needs for modern contraception and unintended pregnancy in Nepal: a cross-sectional study using propensity score matching. Sekine K, Carandang RR, Ong KIC, Tamang A, Jimba M. BMJ Open. 2021 Apr 24;11(4):e043532.
17. EMBRACE intervention to improve the continuum of care in maternal and newborn health in Ghana: The RE-AIM framework-based evaluation. Kikuchi K, Gyapong M, Shibanuma A, Asah E, Okawa S, Addei S, Nanishi K, Tawiah C, Yasuoka J, Yeji F, Oduro A, Owusu-Agyei S, Quansah-Asare G, Hodgson A, Jimba M; Ghana EMBRACE Implementation Research Team. J Glob Health. 2021 Mar 27;11:04017.
18. Rapidly modifiable factors associated with full vaccination status among children in Niamey, Niger: A cross-sectional, random cluster household survey. Kondo Kunieda M, Manzo ML, Shibanuma A, Jimba M. PLoS One. 2021 Mar 31; 16(3):e0249026.
19. Satisfaction of Malaria Patients with Care by Community Health Workers Trained in Microscopy: A Mixed-Methods Study in Palawan, the Philippines. Akiko Matsumoto-Takahashi EL, Tongol-Rivera P, Villacorte EA, Angluben RU, Jimba M, Kano S. Am J Trop Med Hyg. 2021 Mar 22:tpmd190507. doi: 10.4269/ajtmh.19-0507.
20. Japanese health and safety information for overseas visitors: protocol for a randomized controlled trial. Nishikawa M, Yamanaka M, Shibanuma A, Kiriya J, Jimba M. BMC Public Health. 2021 Mar 21;21(1):558.
21. Assessing depressive symptoms among people living with HIV in Yangon city, Myanmar: Does being a member of self-help group matter? Than MW, Zaw NT, Minn K, Saw YM, Kiriya J, Jimba M, Win HH, Shibanuma A. PLoS One. 2021 Mar 18;16(3):e0248807.
22. Parent-adolescent communication on sexual and reproductive health and the utilization of adolescent-friendly health services in Kailali, Nepal. Bhatta BR, Kiriya J, Shibanuma A, Jimba

M. PLoS One. 2021 Feb 19;16(2):e0246917.

23. 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. Takeuchi H, Hasan SMT, Zaman K, Takanashi S, Hore SK, Yeasmin S, Ahmad SM, Alam MJ, Jimba M, Iwata T, Khan MA. Respir Res. 2021 Feb 3; 22(1):35.
24. Parental migration and psychological well-being of left-behind adolescents in Western Nepal. Kharel M, Shibanuma A, Kiriya J, Ong KIC, Jimba M. PLoS One. 2021 Jan 28;16(1): e0245873.
25. Factors associated with breast cancer screening intention in Kathmandu Valley, Nepal. Bhandari D, Shibanuma A, Kiriya J, Hirachan S, Ong KIC, Jimba M. PLoS One. 2021 Jan 22;16(1): e0245856.
26. Nurse-Led Mobile Phone Voice Call Reminder and On-Time Antiretroviral Pills Pick-Up in Nepal: A Randomized Controlled Trial. Ayer R, Poudel KC, Kikuchi K, Ghimire M, Shibanuma A, Jimba M. AIDS Behav. 2021 Jan 3;25(6): 1923-1934.

International Health

2. International Biomedical Sciences

Department of Human Genetics

Professor

Akihiro Fujimoto, Ph.D.

Homepage http://www.humgenet.m.u-tokyo.ac.jp/index.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. Fujimoto, A. et al. Whole-genome sequencing with long reads reveals complex structure and origin of structural variation in human genetic variations and somatic mutations in cancer. **Genome Medicine** 13(1) 65-65 (2021).
2. Mizuno, K. et al. Clinical impact of detecting low-frequency variants in cell-free DNA on treatment of castration-resistant prostate cancer. **Clinical cancer research** (2021)
3. Mizuno, S. et al. Immunogenomic pan-cancer landscape reveals immune escape mechanisms and immunoediting histories **SCIENTIFIC REPORTS 11(1)** (2021).
4. Ashouri, S. et al. Characterization of intermediate-sized insertions using whole-genome sequencing data and analysis of their functional impact on gene expression. **Human Genetics** (2021).

Department of Developmental Medical Sciences

Professor

Masashi Mizuguchi, M.D., Ph.D.

Associate Professor

Teruyuki Tanaka, M.D., Ph.D.

Research Associate

Sayaka Takanashi, M.D., Ph.D. Ai Hoshino, M.D., Ph.D.

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Introduction and Organization

Founded in 1966 as the Department of Maternal and Child Health, our department was the first one established in Japan. With the subsequent expansion of research activities and the foundation of the Graduate School of Medicine, it was renamed in 1998 as the Department of Developmental Medical Sciences. Up to now, it has been engaged in experimental and epidemiologic studies to provide the scientific bases for all the activities to promote the physical and mental health of mothers and children. The experimental studies include those on the nervous and endocrine systems, infection, immunity and metabolism, whereas the epidemiologic studies deal with development, mother-to-child relationship, vaccination and health promotion. In 2007, joined by new members, the department has entered a new era, putting more emphasis than ever on the research on developmental disorders of the human nervous system.

At present, our department consists of one professor, one associate professor, two research associates, one assistant clerk, one technical assistant, seventeen visiting lecturers, fifteen visiting researchers, and eight graduate students (including one overseas student) and one research student.

Our department gives lectures to undergraduate and postgraduate students, have weekly meetings of the whole department and of individual research groups, communicate with other investigators inside or outside the University of Tokyo, and have seminars and meetings with researchers invited from abroad.

We have collaborated with many laboratories in the United States, Canada, Brazil, Italy, Greece, China, Taiwan, Korea, Thailand, Viet Nam, Laos, Malaysia, Myanmar, Indonesia, Bangladesh, Pakistan, Sri Lanka and Australia, in order to promote the mothers' and children's health all over the world. We also have accepted many young students from these countries, for the purpose of bringing up professionals who either perform medical research or lead local health policies.

Teaching activities

1. Undergraduate course, Faculty of Medicine, School of Integrated Health Sciences

   1) Human growth and development
   2) Immunity and defense mechanism
   3) Infectious diseases
   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) 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.

(2) Pharmacological studies on the pathogenesis and treatment of developmental disorders, such as autism spectrum disorder and attention deficit/hyperactivity disorder, using genetically engineered animals.

(3) Medical genetic studies on congenital anomalies caused by abnormal intracellular signal transduction, such as tuberous sclerosis, Noonan syndrome and Ellis-van Creveld syndrome.

(4) Molecular pathologic and translational studies on childhood intractable epilepsy and developmental disorders, such as CDKL5 deficiency disorder, using genetically engineered animals.

(5) Molecular genetic and cell biologic studies combined with post-genomic approaches on molecules regulating neuronal migration, such as Doublecortin and Cdk5.

(6) Studies on the nutrition, immunity, brain and epigenetics of human fetuses and neonates.

(7) International studies on the maternal and child health.

(8) Studies on the virulence, drug resistance and vaccines of herpesviruses and poxviruses.

(9) Molecular epidemiology of pediatric viral infections, in particular gastrointestinal diseases (rotavirus, norovirus, sapovirus and bocavirus), respiratory infections (influenza, RS virus and rhinovirus), exanthematous diseases (rubella) and HIV infection.

References

1. Hoque SA, Khandoker N, Thongprachum A, Khamrin P, Takanashi S, Okitsu S, et al. Distribution of rotavirus genotypes in Japan from 2015 to 2018: Diversity in genotypes before and after introduction of rotavirus vaccines. Vaccine. 2020;38(23):3980-6.
2. Kasai M, Shibata A, Hoshino A, Maegaki Y, Yamanouchi H, Takanashi JI, et al. Epidemiological changes of acute encephalopathy in Japan based on national surveillance for 2014-2017. Brain Dev. 2020; 42(7):508-14.
3. Nguyen PHA, Yamada S, Shibamura M, Inagaki T, Fujii H, Harada S, et al. New Mechanism of Acyclovir Resistance in Herpes Simplex Virus 1, Which Has a UAG Stop Codon between the First and Second AUG Initiation Codons. Jpn J Infect Dis. 2020;73(6):447-51.
4. Okitsu S, Khamrin P, Takanashi S, Thongprachum A, Hoque SA, Takeuchi H, et al. Molecular detection of enteric viruses in the stool samples of children without diarrhea in Bangladesh. Infect Genet Evol. 2020;77:104055.
5. Shibamura M, Yoshikawa T, Yamada S, Inagaki T, Nguyen PHA, Fujii H, et al. Association of human cytomegalovirus (HCMV) neutralizing antibodies with antibodies to the HCMV glycoprotein complexes. Virol J. 2020;17(1):120.
6. Shibata A, Kasai M, Terashima H, Hoshino A, Miyagawa T, Kikuchi K, et al. Case-control association study of rare nonsynonymous variants of SCN1A and KCNQ2 in acute encephalopathy with biphasic seizures and late reduced diffusion. J Neurol Sci. 2020;414:116808.

Department of Human Ecology

Professor

Masahiro UMEZAKI, Ph.D.

Associate Professor

Shoko KONISHI, Ph.D.

Research Associates

Satoko KOSAKA, Ph.D.

Lena TAKAYASU, Ph.D.

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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 as of 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 2021, the Department had four faculty members: Drs. Umezaki, Konishi, Kosaka, and Takayasu. The Department also had 14 visiting lecturers for both graduate or undergraduate courses. Professor Umezaki held additional roles in the Earth Observation Data Integration and Fusion Research Initiative (EDITORIA) at the University of Tokyo.

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. 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 providing 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, 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

Field surveys were conducted annually in the same villages in West Java, Indonesia. Although we did not conduct a field survey in 2021, we performed further analysis and discussion of previously collected data.

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. A questionnaire survey was conducted to gather information regarding lifestyle and sexual function. Urine and semen specimens were collected. The urinary concentrations of elements (cadmium, selenium, etc.) and phthalate esters were measured. Sperm mitochondrial DNA copy number was also measured. Urinary isoflavone and paraben concentrations will be measured.

Additionally, the IITEF project administered a large-scale online questionnaire survey targeting 8,000 men living across Japan. The participants were males aged 20 to 54 years who responded to questions on socioeconomic status and sexual behavior. The findings have been reported at academic conferences.

5. Health transition in Lao People's Democratic Republic

The diet in the northern parts of Laos has been characterized by the consumption of large amounts of rice with dishes made of wild plants. Wild plants with bitter and even astringent tastes, which are supposed to contain more phytochemicals, are preferred over domesticated vegetables. Phytochemicals are suspected to play a role in nutritional adaptation among local people through their interactions with intestinal bacteria. As people have gradually become involved in the market economy, their diet has changed toward more consumption of animal meat and oil, and less consumption of phytochemicals. Our research project investigated the potential health impacts of such dietary changes in northern Laos. The questionnaire survey and sampling of biological specimens were conducted in three communities in the Oudomxay Province (one peri-urban and two farming communities). By evaluating biomarkers of oxidative stress, chronic inflammation, and gut microbiota composition in three communities at different levels of modernization, we sought to clarify the biological link between dietary transition and the recent emergence of noncommunicable diseases in rural Laos. To examine the phytochemical intake from wild plants, we 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. Mouse gut microbiome transitions

The gut microbiome and aging have been discussed based on the average flora of people of different ages. Few studies have been conducted on the

microbiome of the same individual over a long period of time. We conducted experiments on mice from shortly after birth to just before death to determine the changes in the gut microbiome related to pregnancy and lifespan. There are certain phylogenetic trends in bacteria that persist in the gut for long periods, and these persistent microbes are thought to relate strongly to host homeostasis.

8. Determinants of chronic inflammation in rural population 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 city, Nagasaki), 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.

References

1. Kosaka S, Nakao R, Ohnishi M, Umezaki M. The proportion of older population in Nagasaki, Japan, is higher in areas with poor walkability and accessibility. Jpn J Health Hum Ecol. 2021;87:237-245.
2. Mizuno Y, Konishi S, Imai H, Fujimori E, Kojima N, Kajiwara C, Yoshinaga J. Telomere length and urinary 8-hydroxy-2′-deoxyguanosine and essential trace element concentrations in female Japanese university students. J Environ Sci Health A Tox Hazard Subst Environ Eng. 2021;56(12):1328-1334.
3. Mizuno Y, Shimizu-Furusawa H, Konishi S, Inaoka T, Ahmad SA, Sekiyama M, Abdoellah OS, Gunawan B, Parajuli RP, Ikemoto Y, Lam TD, Watanabe C, Umezaki M. Associations between urinary heavy metal concentrations and blood pressure in residents of Asian countries. Environ Health Prev Med. 2021;26(1):101.
4. Mizuno Y, Masuoka H, Kibe M, Kosaka S, Natsuhara K, Hirayama K, Kounnavong NIS, Tomita S, Umezaki M. Impact of modernization on urinary concentrations of arsenic, cadmium, lead, and selenium in rural residents of Northern Laos. Am J Hum Biol. 2021;34(4): e23685.
5. Konishi S, Kariya F, Hamasaki K, Takayasu L, Ohtsuki H. Fecundability and sterility by age: Estimates using time to pregnancy data of Japanese couples trying to conceive their first child with and without fertility treatment. Int J Environ Res Public Health 2021;18(10): 5486.
6. Mizuno Y, Hur K, and Umezaki M. Assessment of intra- and inter-assay variation in dried blood spot telomere length measurements by qPCR. Anthropol Sci. 2021;129(1)99-102.
7. Mizuno Y, Konishi S, Goto C, Yoshinaga J, Hidaka M, Imai H. Association between nutrient intake and telomere length in Japanese female university students. Biomarkers 2021;1-34.
8. Khasnobish A, Takayasu L, Watanabe KI, Nguyen TT, Arakawa K, Hotta O, Joh K, Nakano A, Hosomi S, Hattori M, Suda W. Dysbiosis in the salivary microbiome associated with IgA nephropathy: A Japanese cohort study. Microbes Environ 2021; 36(2):ME21006.
9. Suda W, Ogata Y, Takayasu L, Shindo C, Watanabe K. Complete genome and plasmid sequences of three fluviibacter phosphoraccumulans polyphosphate-accumulating bacterioplankton strains isolated from surface river water. Microbiol Resour Announc 2021;10(9):e01474-20.

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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 dihydroorotate 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

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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, Asakura K, Masayasu S, Sasaki S. Diet-related greenhouse gas emissions and major food contributors among Japanese adults: comparison of different calculation methods. Public Health Nutr 2021; 24(5): 973-83.
2. Tajima R, Murakami K, Asakura K, Fujiwara A, Uechi K, Sugimoto M, Wang HC, Masayasu S, Sasaki S. Snacking in Japanese nursery-school children aged 3-6 years: its characteristics and contribution to overall dietary intake. Public Health Nutr 2021; 24(5): 1042-51.
3. Ohfuji S, Matsuura T, Tamori A, Kubo S, Sasaki S, Kondo K, Ito K, Fukushima W. Lifestyles Associated with Prognosis After Eradication of Hepatitis C Virus: A Prospective Cohort Study in Japan. Dig Dis Sci 2021; 66(6): 2118-28.
4. Shinozaki N, Yuan X, Murakami K, Sasaki S. Development, validation and utilisation of dish-based dietary assessment tools: a scoping review. Public Health Nutr 2021; 24(2): 223-42.
5. Kobayashi Y, Ohfuji S, Kondo K, Fukushima W, Sasaki S, Kamata N, Yamagami H, Fujiwara Y, Suzuki Y, Hirota Y. Association of Dietary Fatty Acid Intake With the Development of Ulcerative Colitis: A Multicenter Case-Control Study in Japan. Inflamm Bowel Dis 2021; 27: 617-28.
6. Miyake Y, Tanaka K, Okubo H, Sasaki S, Tokinobu A, Arakawa M. Maternal metal intake during pregnancy and childhood behavioral problems in Japan: the Kyushu Okinawa Maternal and Child Health Study. Nutr Neurosci 2021; : Online ahead of print.
7. Murakami K, Livingstone B, Masayasu S, Sasaki S. Eating patterns in a nationwide sample of Japanese aged 1-79 years from MINNADE study: eating frequency, clock time for eating, time spent on eating and variability of eating patterns Public Health Nutr 2021; 3(5): 1-13.
8. Okuda M, Fujiwara A, Sasaki S. Composition of Dietary Fatty Acids and Health Risks in Japanese Youths. Nutrients 2021; 13: 426.
9. Sari DW, Noguchi-Watanabe M, Sasaki S, Sahar J, Yamamoto-Mitani N. Estimation of sodium and potassium intakes assessed by two 24-hour urine collections in a city of Indonesia. Br J Nutr 2021; 126(10): 1537-48.
10. Miyake Y, Tanaka K, Okubo H, Sasaki S, Tokinobu A, Arakawa M. Maternal consumption of soy and isoflavones during pregnancy and risk of childhood behavioural problems: the Kyushu Okinawa Maternal and Child Health Study. Int J Food Sci Nutr 2021; 72: 1118-27.
11. Okuda M, Sasaki S. Assessment of foods associated with sodium and potassium intake in Japanese youths using the brief-type self-administered diet history questionnaire. Nutrients 2021; 13(7): 2345.
12. Nishida Y, Nakamura H, Sasaki S, Shirahata T, Sato H, Yogi S, Yamada Y, Nakae S, Tanaka S, Katsukawa F. Evaluation of energy intake by brief-type self-administered diet history questionnaire among male patients with stable/at risk for chronic obstructive pulmonary disease. BMJ Open Respir Res 2021; 8(1): e000807.
13. Oono F, Matsuura N, Saito A, Fujiwara A, Takahashi O, Sasaki S, Iida K. Association of Hours of Paid Work with Dietary Intake and Quality in Japanese Married Women: A Cross-Sectional Study. Nutrients 2021; 13(9): 3005.
14. Ishikawa-Takata K, Nakae S, Sasaki S, Katsukawa F, Tanaka S. Age-Related Decline in Physical Activity Level in the Healthy Older Japanese Population. J Nutr Sci Vitaminol (Tokyo) 2021; 67: 330-8.
15. Fukuoka S, Arita R, Mizoguchi T, Kawashima M, Koh S, Shirakawa R, Suzuki T, Sasaki S, Morishige N. Relation of Dietary Fatty Acids and Vitamin D to the Prevalence of Meibomian Gland Dysfunction in Japanese Adults: The Hirado-Takushima Study. J Clin Med 2021; 10: 350.

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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. Aso S, Matsui H, Fushimi K, Yasunaga H. Dexmedetomidine and mortality from sepsis requiring mechanical ventilation. Journal of Intensive Care Medicine. 2021;36(9):1036-1043
2. Chinen T, Sasabuchi Y, Matsui H, Yasunaga H. Association between third-generation fluoroquinolones and Achilles tendon rupture: a self-controlled case series analysis. Annals of Family Medicine. 2021;19(3):212-216.
3. Awano N, Jo T, Yasunaga H, Inomata M, Kuse N, Tone M, Morita K, Matsui H, Fushimi K, Nagase T, Izumo T. Body mass index and in-hospital mortality in patients with acute exacerbation of idiopathic pulmonary fibrosis. ERJ Open Research. 2021;7(2):00037-2021.
4. Enomoto Y, Iwagami M, Tsuchiya A, Morita K, Abe T, Kido T, Uda K, Inokuchi R, Yasunaga H, Inoue Y, Tamiya N. Dexmedetomidine use and mortality in mechanically ventilated patients with severe burns: a cohort study using a national inpatient database in Japan. Burns. 2021;47(7): 1502-1510.
5. Hamada S, Nakajima M, Kaszynski RH, Kumazawa R, Matui H, Fushimi K, Goto H, Yamaguchi Y, Yasunaga H. In-hospital mortality among patients with invasive non-group A β-hemolytic Streptococcus treated with clindamycin combination therapy: A nationwide cohort study. Acute Medicine & Surgery. 2021; 8(1):e634.
6. Hasegawa S, Okada A, Aso S, Kumazawa R, Matsui H, Fushimi K, Yasunaga H, Nangaku M. Association between diabetes and major bleeding complications of renal biopsy. Kidney International Reports. 2021;7(2):232-240.
7. Hashimoto Y, Michihata N, Yamana H, Shigemi D, Morita K, Matsui H, Yasunaga H, Aihara M. Intraocular pressure-lowering medications during pregnancy and risk of neonatal adverse outcomes: a propensity score analysis using a large database. British Journal of Ophthalmology. 2021;105(10):1390-1394.
8. Hashimoto Y, Michihata N, Matsui H, Ishimaru M, Fushimi K, Yasunaga H, Aihara M, Takao M, Obata R. Recent trends in vitreoretinal surgery: a nationwide database study in Japan, 2010–2017. Japanese Journal of Ophthalmology. 2021;65(1): 54-62
9. Hatachi T, Michihata N, Inata Y, Takeuchi M, Matsui H, Fushimi K, Yasunaga H. Prognostic factors among children with acute encephalitis/encephalopathy associated with viral and other pathogens. Clinical Infectious Disease. 2021; 73(1):76-82.
10. Hattori Y, Tahara S, Aso S, Matsui H, Fushimi K, Yasunaga H, Morita A. Prophylactic steroid administration and complications after transsphenoidal pituitary surgery: a nationwide inpatient database study in Japan. British Journal of Anaesthesia. 2021;127(2):e41-e43.
11. Hirose N, Morita K, Nakamura M, Fushimi K, Yasunaga H. Association between the duration of physical restraint and pulmonary embolism in psychiatric patients: A nested case–control study using a Japanese nationwide database. Archives of Psychiatric Nursing 2021;35(5):534-540.
12. Hirose N, Morita M, Jo T, Hagiwara Y, Matsui H, Fushimi K, Yasunaga H. Differences in disease severity and in-hospital mortality in patients hospitalized for pneumonia with and without intellectual disability: A matched-pair retrospective cohort study using nationwide in-patient database. Journal of Intellectual & Developmental Disability. 2021;47(1):65-73.
13. Honda A, Michihata N, Iizuka Y, Mieda T, Takasawa E, Ishiwata S, Matsui H, Fushimi K, Yasunaga H, Chikuda H. Clinical features and post-treatment complications of isolated C2 odontoid fractures: a retrospective analysis using a national inpatient database in Japan. European Spine Journal. 2021;30(12):3631-3638.
14. Hoshina K, Kato M, Ishimaru S, Michihata N, Yasunaga H, Komori K, Japanese Committee for Stentgraft Management. Effect of the urgency and landing zone on rates of in-hospital death, stroke, and paraplegia after thoracic endovascular aortic repair in Japan. Journal of Vascular Surgery. 2021;74(2):556-568.e2.
15. Ikawa F, Isobe N, Michihata N, Oya S, Ohata K, Saito K, Yoshida K, Fushimi K, Yasunaga H, Tominaga T, Kurisu K. Inhospital complications after surgery in elderly patients with

asymptomatic or minor symptom meningioma: a nationwide registry study. World Neurosurgery. 2021;148:e459-e470.

16. Itoh H, Kaneko H, Kiriyama H, Kamon T, Fujiu K, Morita K, Michihata N, Jo T, Takeda N, Morita H, Yasunaga H, Komuro I. Metabolically Healthy Obesity and the Risk of Cardiovascular Disease in General Population: Analysis of a Nationwide Epidemiological Database. Circ J 2021;85:914-920
17. Itoh H, Kaneko H, Kiriyama H, Kamon T, Fujiu K, Morita K, Yotsumoto H, Michihata N, Jo T, Takeda N, Morita H, Yasunaga H, Komuro I. Reverse J-shaped relationship between body mass index and in-hospital mortality of patients hospitalized for heart failure in Japan. Heart and Vessels. 2021;36(3):383-392.
18. Itoh H, Kaneko H, Fujiu K, Kiriyama H, Morita K, Kamon T, Michihata N, Jo T, Takeda N, Morita H, Yasunaga H, Komuro I. Risk Factors and Lifestyles in the Development of Atrial Fibrillation Among Individuals Aged 20-39 Years. American Journal of Cardiology. 2021;155: 40-44.
19. Iwagami M, Kumazawa R, Miyamoto Y, Ito Y, Ishimaru M, Morita K, Hamada S, Tamiya N, Yasunaga H. Risk of Cancer in Association with Ranitidine and Nizatidine vs Other H2 Blockers: Analysis of the Japan Medical Data Center Claims Database 2005-2018. Drug Safety. 2021; 44(3):361-371.
20. Jimba T, Kaneko H, Yano Y, Itoh H, Yotsumoto H, Seki H, Morita K, Kiriyama H, Kamon T, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Nishiyama A, Node K, Yasunaga H, Komuro I.Relation of the Metabolic Syndrome to Incident Colorectal Cancer in Young Adults Aged 20 to 49 Years. American Journal of Cardioloy 2021;158: 132−138.
21. Jin X, Tamiya N, Uda K, Yasunaga H. The impact of additional payments on functional decline among long-term care health facility residents in Japan. Age and Ageing. 2021;50(6):2055-2062.
22. Jo T, Michihata N, Yamana H, Morita K, Ishimaru M, Yamauchi Y, Hasegawa W, Urushiyama H, Uda K, Matsui H, Fushimi K, Yasunaga H, Nagase T. Risk of drug-induced interstitial lung disease in hospitalised patients: a nested case–control study. Thorax. 2021;76(12): 1193-1199.
23. Kaneko H, Itoh H, Kamiya K, Morita K, Sugimoto T, Konishi M, Kiriyama H, Kamon T, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Yasunaga H, Komuro I. Acute-Phase Initiation of Cardiac Rehabilitation and Clinical Outcomes in Hospitalized Patients for Acute Heart Failure. Int J Cardiol. 2021;340:36-41.
24. Kaneko H, Yano Y, Itoh H, Morita K, Kiriyama H, Kamon T, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Nishiyama A, Node K, Bakris G, Miura K, Muntner P, Viera AJ, Oparil S, Lloyd-Jones DM, Yasunaga H, Komuro K. Untreated Hypertension and Subsequent Incidence of Colorectal Cancer: Analysis of a Nationwide Epidemiological Database. Journal of American Heart Association. 2021;10(22): e022479.
25. Kaneko H, Yano Y, Itoh H, Morita K, Kiriyama H, Kamon T, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Node K, Carey RM, Lima JAC, Oparil S, Yasunaga H, Komuro I. Association of Blood Pressure Classification Using the 2017 American College of Cardiology/American Heart Association Blood Pressure Guideline With Risk of Heart Failure and Atrial Fibrillation. Circulation. 2021; 143(23):2244-2253.
26. Kaneko H, Itoh H, Yotsumoto H, Kiriyama H, Kamon T, Fujiu K, Morita K, Michihata N, Jo T, Takeda N, Morita H, Yasunaga H, Komuro I. Impact of hospital volume on clinical outcomes of hospitalized heart failure patients: Analysis of a nationwide database including 447,818 patients with heart failure. BMC Cardiovascular Disorders. 2021;21:49
27. Kaneko H, Itoh H, Kiriyama H, Kamon T, Fujiu K, Morita K, Michihata N, Jo T, Takeda N, Morita H, Yasunaga H, Komuro I. Possible association between eating behaviors and cardiovascular disease in the general population: Analysis of a nationwide epidemiological database. Atherosclerosis 2021;320:79-85.
28. Kaneko H, Itoh H, Morita K, Sugimoto T, Konishi M, Kamiya K, Kiriyama H, Kamon T, Fujiu K, Michihata N, Jo T, Takeda N, Morita H,

Yasunaga H, Komuro I. Early Initiation of Feeding and In-hospital Outcomes in Patients Hospitalized for Acute Heart Failure. American Journal of Cardiology 2021;145:85-90.

29. Kaneko H, Itoh H, Kiriyama H, Kamon T, Fujiu K, Morita K, Michihata N, Jo T, Takeda N, Morita H, Yasunaga H, Komuro I. Lipid Profile and Subsequent Cardiovascular Disease among Adults Aged < 50 Years. American Journal of Cardiology 2021;142:59-65.
30. Kaneko H, Itoh H, Kiriyama H, Kamon T, Fujiu K, Morita K, Michihata N, Jo T, Takeda N, Morita H, Yasunaga H, Komuro I. Fasting plasma glucose and subsequent cardiovascular disease among young adults: Analysis of a nationwide epidemiological database. Atherosclerosis 2021; 319:35-41.
31. Kaneko H, Itoh H, Yotsumoto H, Kiriyama H, Kamon T, Fujiu K, Morita K, Kashiwabara K, Michihata N, Jo T, Morita H, Yasunaga H, Komuro I. Cardiovascular Health Metrics of 87,160 Couples: Analysis of a Nationwide Epidemiological Database. Journal of Atherosclerosis and Thrombosis. 2021;28(5):535-543.
32. Katsuki R, Jo T, Yasunaga H, Ishimaru M, Sakamoto T. Outcomes of Self-expandable Metal Stent as Bridge to Surgery versus Emergency Surgery for Left-sided Obstructing Colon Cancer: A Retrospective Cohort Study. Am J Surg. 2021; 221(1):168-173.
33. Katsuki Y. Jo T, Yasunaga H, Kumazawa R, Uda K. Outcomes of Laparoscopic versus Open Pancreatoduodenectomy: A Nationwide Retrospective Cohort Study. Surgery. 2021;169(6): 1427-1433.
34. Kawata M, Taketomi S, Inui H, Matsui H, Fushimi K, Yamagami H, **Yasunaga H**, Tanaka S. Type of bone graft and primary diagnosis were associated with nosocomial surgical site infection after high tibial osteotomy: analysis of a national database. Knee Surgery, Sports Traumatology, Arthroscopy. 2021;29(2):429-436.
35. Kim HS, Cheng HS, Yamana H, Lee S, Yoon NH, Lin YC, Fushimi K, Yasunaga H. Variations in Hip Fracture Inpatient Care in Japan, Korea, and Taiwan: An Analysis of Health Administrative Data. BMC Health Services Research. 2021; 21(1):694.
36. Kiriyama H, Kaneko H, Itoh H, Kamon T, Morita K, Jo T, Fujiu K, Daimon M, Takeda N, Morita H, Yasunaga H, Komuro I. Surgical Treatment for Infective Endocarditis in the Aging Society: a Nationwide Retrospective Study in Japan. Open Heart. 2021;8(1):e001627.
37. Kitamura T, Nakajima M, Kawamura I, Kaszynski RH, Ohbe H, Sasabuchi Y, Matsui H, Fushimi K, Fukamizu S, Yasunaga H. Safety and effectiveness of intracardiac echocardiography in ventricular tachycardia ablation: A nationwide observational study. Heart and Vessels. 2021; 36(7):1009-1015.
38. Koizumi M, Ishimaru M, Matsui H, Fushimi K, Yamasoba T, Yasunaga H. Factors associated with the occurrence of stomal stenosis after tracheostomy in adults. Auris Nasus Larynx. 2021;48(5):973-977.
39. Kondo Y, Ohbe H, Aso S, Matsui H, Fushimi K, Tanaka H, Yasunaga H. Efficacy of prophylactic antibiotics during extracorporeal membrane oxygenation: A nationwide cohort study. Annals of the American Thoracic Society. 2021;18(11): 1861-1867.
40. Konishi T, Fujiogi M, Michihata N, Kumazawa R, Matsui H, Fushimi K, Tanabe M, Seto Y, Yasunaga H. Outcomes of nonoperative treatment for gastroduodenal ulcer perforation: a nationwide study of 14,918 inpatients in Japan. Journal of Gastrointestinal Surgery 2021;25(11): 2770-2777
41. Konishi T, Fujiogi M, Michihata M, Morita K, Matsui H, Fushimi K, Tanabe M, Seto Y, Yasunaga H. Association between body mass index and localization of breast cancer: results from a nationwide inpatient database in Japan. Breast Cancer Research and Treatment. 2021; 185(1):175-182.
42. Konishi T. Fujiogi M, Michihata N, Morita K, Matsui H, Fushimi K, Tanabe M, Seto Y, Yasunaga H. Comparison of short-term surgical outcomes between men and women with breast cancer: a retrospective study using nationwide inpatient data in Japan. Breast Cancer Research and Treatment. 2021;186(3):731-739.

43. Konishi T, Fujiogi M, Michihata N, Morita K, Matsui H, Fushimi K, Tanabe M, Seto Y, Yasunaga H. Comparing outcomes of non-operative treatment for adhesive small bowel obstruction with and without antibiotics. Journal of Infection and Chemotherapy. 2021;27(5):690-695.
44. Konishi T, Fujiogi M, Michihata N, Morita K, Matsui H, Fushimi K, Tanabe M, Seto Y, Yasunaga H. Comparisons of postoperative outcomes after breast cancer surgery in patients with and without renal replacement therapy: a matched-pair cohort study using a Japanese nationwide inpatient database. Breast Cancer. 2021;28(5):1112-1119.
45. 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. European Thyroid Journal. 2021; 11(1):e210081.
46. Konishi T, Fujiogi M, Michihata N, Tanaka-Mizutani H, Morita K, Matsui H, Fushimi K, Tanabe M, Seto Y, Yasunaga H. Breast cancer surgery in patients with schizophrenia: short-term outcomes from a nationwide cohort. British Journal of Surgery. 2021;108:168–173.
47. Kurakawa K, Okada A, Manaka K, Konishi T, Jo T, Ono S, Uda K, Michihata N, Matsui H, Fushimi K, Yamaguchi S, Yamauchi T, Nangaku M, Yasunaga H, Kadowaki T. Clinical characteristics and incidences of benign and malignant insulinoma using a national inpatient database in Japan. Journal of Clinical Endocrinology & Metabolism. 2021;106(12): 3477-3486.
48. Makito K, Matsui H, Fushimi K, Yasunaga H. Spinal epidural hematoma and abscess after neuraxial anesthesia: a historical cohort study using the Japanese Diagnosis Procedure Combination database. Canadian Journal of Anesthesia. 2021;68(1):42-52.
49. Matsuda K, Jo T, Toyama K, Nakazaki K, Matsui H, Fushimi K, Yasunaga H. Efficacy of recombinant human soluble thrombomodulin in induction therapy for acute promyelocytic leukemia. Thrombosis Research. 2021;202:173-175.
50. Matsuda K, Ise M, Shimura A, Honda A, Masamoto Y, Jo T, Yasunaga H, Kurokawa M. Use of wide-spectrum antimicrobials with blood culture tests during chemotherapy as an accurate marker of febrile neutropenia in the DPC database: A validation study. Journal of Infection and Chemotherapy. 2021;27(10):1541-1542.
51. Matsuda K, Jo T, Toyama K, Nakazaki K, Matsui H, Fushimi K, Yasunaga H, Kurokawa M. Risk factors for early in-hospital death in patients who developed coagulopathy during induction therapy for acute promyelocytic leukemia: a nation-wide analysis in Japan. Annals of Hematology. 2021; 100(10):2613-2619.
52. Matsuda K, Jo T, Miyauchi M, Toyama K, Nakazaki K, Matsui H, Fushimi K, Yasunaga H, Kurokawa M. Difference of preventing effects of G-CSF according to age in patients with malignant lymphoma: a nation-wide analysis in Japan. Journal of Infection and Chemotherapy. 2021;27(8):1151-1155.
53. Matsuzaki S, Kaneko H, Yano Y, Itoh H, Fukui A, Morita M, Kiriyama H, Kamon T, Fujiu K, Seki H, Michihata N, Jo T, Takeda N, Morita H, Nakamura S, Yokoo T, Nishiyama A, Node K, Yasunaga H, Komuro I. Association Between Blood Pressure Classification Using the 2017 ACC/AHA Blood Pressure Guideline and Retinal Atherosclerosis. American Journal of Hypertension. 2021;34(10):1049-1056.
54. Miyamoto Y, Ohbe H, Ishimaru M, Matsui H, Fushimi K, Yasunaga H. Effect of tranexamic acid in patients with colonic diverticular bleeding: a nationwide inpatient database study. Journal of Gastroenterology and Hepatology 2021;36(4):999-1005.
55. Miyamoto Y, Ohbe H, Goto T, Yasunaga H. Association between intensive care unit admission of a patient and mental disorders in the spouse: a retrospective matched-pair cohort study. Journal of Intensive Care. 2021;9(1):69.
56. Miyano S, Michihata N, Sada K, Uda K, Matsui H, Fushimi K, Nangaku M, Yasunaga H. Comparison of fracture risk between proton

pump inhibitors and histamine-2 receptor antagonists in AAV patients: A nested case-control study. Rheumatology. 2021;60(4):1717-1723.

57. Mizuno S, Sachiko Ono 2, Hideo Yasunaga 3, Hirotaro Iwase 4. Factors associated with methamphetamine use in Japanese people who died of unnatural causes: Analysis using forensic autopsy reports. Forensic Science International. 2021;327:110946.
58. Mongkonchoo K, Yamana H, Aso S, Machidad M, Takasaki Y, Jo T, Yasunaga H, Chongsuvivatwong Y, Liabsuetrakul T. Prediction of outpatient visits and expenditure under the Universal Coverage Scheme in Bangkok using subscriber's attributes: a random forest analysis. Public Health in Practice. 2021;2:100190.
59. Morita K, Fukahori H, Ogawara H, Iwagami M, Matsui H, Okura T, Itoh S, Fushimi K, Yasunaga H. Outcomes of a financial incentive scheme for dementia care by dementia specialist teams in acute-care hospitals: a difference-in-differences analysis of a nationwide retrospective cohort study in Japan. International Journal of Geriatric Psychiatry. 2021;36(9):1386-1397.
60. Nakamura K, Ohbe H, Ikeda K, Uda K, Furuya H, Furuta S, Nakajima M, Sasabuchi Y, Matsui H, Fushimi K, Yasunaga H, Nakajima H. Intravenous cyclophosphamide in acute exacerbation of rheumatoid arthritis-related interstitial lung disease: a propensity-matched analysis using a nationwide inpatient database. Seminars in Arthritis and Rheumatism. 2021; 51(5):977-982.
61. Naruse K, Shigemi D, Hashiguchi M, Imamura M, Yasunaga H, Arai T. Placental abruption in each phenotype of hypertensive disorders of pregnancy: a retrospective cohort study using a national inpatient database in Japan. Hypertension Research. 2021;44(2):232-238.
62. Nozawa H, Ishizawa T, Yasunaga H, Ishii H, Sonoda H, Emoto S, Murono K, Sasaki K, Kawai K, Akamatsu N, Kaneko J, Arita J, Hasegawa K, Ishihara S. Open and/or laparoscopic one-stage resections of primary colorectal cancer and synchronous liver metastases –an observational study. Medicine. 2021;100(11):e25205.
63. Oda K, Aso S, Hattori Y, Yamaguchi F, Matsui H, Fushimi K, Yasunaga H, Morita A. Snowfall reduces the risk of chronic subdural hematoma onset: Analysis of an administrative database in Japan. Surgial Neurology International 2021;12: 69.
64. Ohbe H, Nakamura K, Uda K, Matsui H, Yasunaga H. Effect of early rehabilitation on physical function in patients undergoing coronary artery bypass grafting: a nationwide inpatient database study. Journal of Clinical Medicine 2021;10(4):618
65. Ohbe H, Matsui H, Fushimi K, Yasunaga H. Small-bore feeding tube versus large-bore sump tube for early enteral nutrition in mechanically ventilated patients: a nationwide inpatient database study. Clinical Nutrition. 2021;40(6): 4113-4119.
66. Ohbe H, Matsui H, Fushimi K, **Yasunaga H**. Epidemiology of Chronic Critical Illness in Japan: A Nationwide Inpatient Database Study. Crit Care Med 2021;49(1):70-78
67. Ohbe H, Jo T, Matsui H, Fushimi K, **Yasunaga H**. Clinical trajectories of suicide attempts and self-harm in patients admitted to acute-care hospitals in Japan: a nationwide inpatient database study. Journal of Epidemiology. 2021; 31(3):231-236.
68. Ohbe H, Sasabuchi Y, Yamana H, Matsui H, Yasunaga H. Intensive care unit versus high-dependency care unit for mechanically ventilated patients with pneumonia: a nationwide comparative effectiveness study. The Lancet Regional Health - Western Pacific. 2021;13: 100185.
69. Ohbe H, Yasunaga H. Spouse's cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a matched-pair cohort study. Circulation: Cardiovascular Quality and Outcomes. 2021;14(8):e007649.
70. Ohbe H, Iwagami M, Sasabuchi Y, Yasunaga H. Increased risk of infective endocarditis after traumatic skin wound. Heart. 2021;107(23):1868-1874
71. Ohbe H, Jo T, Matsui H, Fushimi K, Yasunaga H. Effect of Daikenchuto for mechanically ventilated patients with enteral feeding

intolerance: a propensity score-matched analysis using a nationwide administrative inpatient database. Journal of Parenteral and Enteral Nutrition. 2021;45(8):1703-1713

72. Ohbe H, Matsui H, Yasunaga H. Intensive care unit versus high-dependency care unit for patients with acute heart failure: a nationwide propensity score-matched cohort study. J Intensive Care. 2021;9(1):78.
73. Ohbe H, Yamana H, Matsui H, Yasunaga H. Development and validation of a procedure-based organ failure assessment model for patients in the intensive care unit: an administrative database study. Acute Medicine & Surgery. 2021;8(1): e719.
74. Okada A, Ono S, Yamaguchi S, Yamana H, Kurakawa K, Michihata N, Matsui H, Nangaku M, Yamauchi T, Yasunaga H, Kadowaki T. Association between nutritional guidance or ophthalmological examination and discontinuation of physician visits in patients with newly diagnosed diabetes: a retrospective cohort study using a nationwide database. Journal of Diabetes Investigation. 2021;12(9):1619-1631.
75. Okada A, Yamana H, Morita K, Sato Y, Yamaguchi S, Kurakawa K, Michihata N, Matsui H, Fushimi K, Nangaku M, Yamauchi T, Yasunaga H, Kadowaki T. Potassium concentration in initial fluid therapy and in-hospital mortality of patients with diabetic ketoacidosis. Journal of Clinical Endocrinology & Metabolism. 2021;106(5):e2162-e2175.
76. Okubo Y, Horimukai K, Michihata N, Morita K, Matsui H, Fushimi K, Yasunaga H. Association between early antibiotic treatment and clinical outcomes in children hospitalized for an asthma exacerbation. Journal of Allergy and Clinical Immunology. 2021:114-122.e14.
77. Okubo Y, Michihata N, Morisaki N, Yoshida K, Matsui H, Fushimi K, **Yasunaga H**. Effects of glucocorticoids on hospitalized children with anaphylaxis. Pediatric Emergency Care. 2021; 37(5):255-259.
78. Ono S, Ishimaru M, Ida Y, Yamana H, Ono Y, Hoshi K, Yasunaga H. Validity of diagnoses and procedures in Japanese dental claims data. BMC Health Services Research. 2021;21(1):1116.
79. Otaka S, Aso S, Matsui H, Fushimi K, Yasunaga H. Association between parenteral nutrition in the early phase and outcomes in patients with abdominal trauma undergoing emergency laparotomy: A retrospective nationwide study. Clinical Nutrition ESPEN 2021;41:371-376
80. Otaka S, Aso S, Matsui H, Fushimi K, Yasunaga H.. Associations between early parenteral nutrition and in-hospital outcomes in underweight patients with gastrointestinal surgery. Clinical Nutrition ESPEN 2021;43:464-470.
81. Sakamoto T, Fujiogi M, Matsui H, Fushimi K, Yasunaga H. Comparing perioperative mortality and morbidity of minimally invasive esophagectomy versus open esophagectomy for esophageal cancer: a nationwide retrospective analysis. Annals of Surgery. 2021;274(2):324-330.
82. Sakamoto Y, Yamauchi Y, Jo T, Michihata N, Hasegawa W, Takeshima H, Matsui H, Fushimi K, Yasunaga H, Nagase T. In-hospital mortality associated with community-acquired pneumonia due to methicillin-resistant Staphylococcus aureus: a matched-pair cohort study. BMC Pulmonary Medicine. 2021;21(1):345.
83. Sako A, Yasunaga H, Matsui H, Fushimi K, Yanai H, Gu Y, Ohmagari N. Hospitalization for Urinary Tract Infections in Japan, 2010–2015: A Retrospective Study Using a National Inpatient Database. BMC Infectious Diseases. 2021;21(1): 1048.
84. Sato D, Goto T, Uda K, Kumazawa R, Matsui H, Yasunaga H. Impact of national guidelines for antimicrobial stewardship to reduce antibiotic use in upper respiratory tract infection and gastroenteritis. Infection Control & Hospital Epidemiology 2021;42:280 – 286
85. Sato Y, Morita K, Okada A, Matsui H, Fushimi K, Yasunaga H. Factors affecting in-hospital mortality of diabetic ketoacidosis patients: A retrospective cohort study. Diabetes Research and Clinical Practice 2021;171:108588.
86. 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. Journal of Orthopaedic Science. 2021;26(4):666-671.

87. Seki M, Kaneko H, Morita H, Itoh H, Morita K, Matsuoka S, Kiriyama H, Kamon T, Fujiu K, Michihata N, Jo T, Takeda N, Yano Y, Nakamura S, Node K, Yasunaga H, Komuro I. Relation of Serum Uric Acid and Cardiovascular Events in Young Adults Aged 20-49 Years. American Journal of Cardiology 2021;152:150-157.
88. Shigemi D, Isogai S, Uda K, Aso S, Matsui H, Fushimi K, **Yasunaga H**. Association between rehabilitation during hospitalization and perinatal outcomes among pregnant women with threatened preterm birth. The Journal of Maternal-Fetal & Neonatal Medicine. 2021; 34(7):1028-1033
89. Shigemi D, Hashimoto Y, Michihata N, Yasunaga H. Effect of Japanese herbal Kampo medicines on live birth rate in women with recurrent pregnancy loss. International Journal of Gynecology and Obstetrics. 2021;153(3):489-495.
90. Shigemi D, Hashimoto Y, Michihata N, Yasunaga H. Impact of maternal depression and anxiety-related disorders on live birth rate in women with recurrent pregnancy loss. Human Fertility. 2021; 20;1-8.
91. Shigemi D, Morishima T, Yamana H, Yasunaga H, Miyashiro I. Validity of initial cancer diagnoses in the Diagnosis Procedure Combination data in Japan. Cancer Epidemiology. 2021;74:102016.
92. Shinozaki N, Morita K, Matsui H, Jo T, Yasunaga H. Semisolid versus liquid nutrients and 30-day readmission in gastrostomy tube-fed patients: a propensity-matched analysis. Journal of Parenteral and Enteral Nutrition. 2021;45(4): 720-728.
93. Shiozawa M, Kaneko H, Itoh H, Morita K, Okada A, Matsuoka S, Kiriyama H, Kamon T, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Nakamura S, Node K, Yasunaga H, Komuro I. Association of Body Mass Index with Ischemic and Hemorrhagic Stroke. Nutrients. 2021;13(7): 2343.
94. Shirane S, Michihata N, Yoshiuchi K, Ariyoshi K, Iwase S, Morita K, Matsui H, Fushimi K, Yasunaga H. Evaluation of quality indicators near death in older adult cancer decedents in Japan: A nationwide retrospective cohort study. Japanese Journal of Clinical Oncology. 2021;51(11)1643–1648.
95. Suzuki T, Michihata N, Aso S, Yoshikawa T, Saito K, Matsui H, Fushimi K, Yasunaga H. Sodium-containing versus sodium-trace preparations of IVIG for children with Kawasaki disease in the acute phase. European Journal of Pediatrics. 2021 ;180(11):3279-3286.
96. Takano A, Yamana H, Ono S, Matsui H, Yasunaga H. Outpatient treatment following alcohol screening at health checkups and change in drinking patterns among excessive drinkers with lifestyle-related diseases. Preventive Medicine Reports. 2021;24:101549.
97. Takiguchi T, Ohbe H, Nakajima M, Sasabuchi Y, Tagami T, Matsui H, Fushimi K, Yokobori S, Yasunaga H. Intermittent versus continuous neuromuscular blockade during target temperature management after cardiac arrest: a nationwide observational study. Journal of Critical Care 2021;62:276-282.
98. Takeuchi Y, Kumamaru H, Hagiwara Y, Matsui H, Yasunaga H, Miyata H, Matsuyama Y. Sodium-glucose cotransporter-2 inhibitors and the risk of urinary tract infection among diabetic patients in Japan: Target trial emulation using a nationwide administrative claims database. Diabetes, Obesity and Metabolism. 2021;23(6): 1379-1388.
99. Tanaka G, Jo T, Tamiya H, Sakamoto Y, Hasegawa W, Matsui H, Fushimi K, Yasunaga H, Nagase T. Factors affecting in-hospital mortality of non-tuberculous mycobacterial pulmonary disease. BMC Infectious Diseases 2021;21:698.
100. Taniguchi K, Ohbe H, Yamakawa K, Matsui H, Fushimi K, Yasunaga H. Recombinant thrombomodulin in disseminated intravascular coagulation associated with stage IV solid tumors: a nationwide observational study in Japan. Thrombosis and Haemostasis. 2021; 121(1):36-45.
101. Tsuchiya A, Tsutsumi Y, Yasunaga H, Yasuda S, Yuzawa K, Kushimoto S. Long-term Functional Outcomes, Quality of Life, and Patient Trajectory

in 1 Trauma Survivors: A Study Protocol. Annals of Clinical Epidemiology. 2021;3(2):59–66.

102. Ugata Y, Michihata N, Matsui H, Fushimi K, Yasunaga H. Impact of proton pump inhibitors on mortality and severe esophageal injury after catheter ablation for atrial fibrillation: a nationwide retrospective study using propensity score matching. Heart and Vessels. 2021;36(11): 1730-1738.
103. Urushiyama H, Jo T, Hasegawa W, Ando T, Sakamoto Y, Uda K, Matsui H, Fushimi K, Yasunaga H, Nagase T. Preoperative use of pirfenidone and reduced risk of postoperative severe respiratory complications in patients with idiopathic pulmonary fibrosis: propensity score-matched analysis using a nationwide database in Japan. Respirology. 2021;26(6):590-596.
104. Yagi M, Morita K, Matsui H, Michihata N, Fushimi K, Koyama T, Fujitani J, Yasunaga H. Outcomes after Intensive Rehabilitation for Mechanically-ventilated Patients: A Nationwide Retrospective Cohort Study. Archives of Physical Medicine and Rehabilitation. 2021;102(2):280-289.
105. Yamamoto N, Ohbe H, Tomita Y, Yorifuji T, Nakajima M, Sasabuchi Y, Miyamoto Y, Matsui H, Noda T, Yasunaga H. Associations between early surgery and postoperative outcomes in elderly patients with distal femur fracture: a retrospective cohort study. Journal of Clinical Medicine. 2021;10(24):5800.
106. Yamana H, Iba A, Tomio J, Ono S, Jo T, Yasunaga H. Treatment of latent tuberculosis infection in patients receiving biologic agents. Journal of Infection and Chemotherapy. 2021; 27(2):243-249.
107. Yamana H, Ono S, Michihata N, Jo T, Yasunaga H. Association between maoto use and hospitalization for seasonal influenza in a nonelderly cohort in Japan. Internal Medicine. 2021;60(21): 3401-3408.
108. Yamana H, Imai S, Yamasaki K, Horiguchi H, Ario K, Komatsu T, Sugimoto R, Katsushima S, Naganuma A, Mano Y, Yamashita T, Kamitsukasa H, Tsuruta S, Jo T, Yasunaga H, Fushimi K, Yatsuhashi H. Prognosis of patients with liver cirrhosis: a multi-center retrospective observational study. Hepatology Research. 2021;51(12): 1196-1206.
109. Yamazaki R, Ohbe H, Matsuda Y, Kito S, Morita K, Matsui H, Fushimi K, Yasunaga H. Early electroconvulsive therapy in patients with major depressive disorder: a propensity score-matched analysis using a nationwide inpatient database in Japan. The Journal of ECT. 2021;37(3):176-181.
110. Yasui H, Michihata N, Matsui H, Fushimi K, Iwase S, Yoshiuchi K, Sakata Y, Yasunaga H. Association between ambulance use and hospitalization costs among heart failure patients. Heart and Vessels. 2021;36(5):654-658.
111. Yokoyama A, Sakamoto Y, Jo T, Urushiyama H, Tamiya H, Tanaka G, Matsui H, Fushimi K, Yasunaga H, Nagase T. Pulmonary disease as a risk factor for transfusion-related acute lung injury. ERJ Open Research. 2021;7(3):00039-2021.
112. Yoshihara S, Yamana H, Akahane M, Kishimoto M, Nishioka Y, Noda T, Matsui H, Fushimi K, Yasunaga H, Kasahara K, Imamura T. Association between Prophylactic Antibiotic Use for Transarterial Chemoembolization and Occurrence of Liver Abscess: A Retrospective Cohort Study. Clinical Microbiology and Infection. 2021; 27(10):1514.e5-1514.e10.
113. Yoshii E, Yamana H, Ono S, Matsui H, Yasunaga H. Association between allergic or autoimmune diseases and incidence of endometriosis: A nested case-control study using a health insurance claims database. Am J Reprod Immunol. 2021; 86(5):e13486.

Department of Health Communication

Professor

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Associate Professor

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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
10. Entertainment education
11. Visual communication
12. Communicating for policy and advocacy
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, Okada H, Goto E, Kiuchi T. Readability assessment of HPV vaccination and cervical cancer information: a systematic scoping review. Healthcare. 2021; 9(10):1246.
2. Okuhara T, Okada H, Goto E, Kiuchi T. Urgent need for writing education in schools of medicine and public health to address vaccine hesitancy. International Journal of Medical Education. 2021; 12:166-168.
3. Okuhara T, Okada H, Kiuchi T. Lessons Learned from a Writing to Learn Program for Public Health Students at the University of Tokyo. Journal of Medical Education and Curricular Development. 2021;8:23821205211032014.
4. Iye R, Okuhara T, Okada H, Yokota R, Kiuchi T. A content analysis of video advertisements for dietary supplements in Japan. Healthcare. 2021; 9(6):742.
5. Okuhara T, Ishikawa H, Ueno H, Okada H, Kiuchi T. Readability assessment of vaccine information: a systematic review for addressing vaccine hesitancy. Patient Education and Counseling. 2021;105(2):331-338.
6. Okada H, Morita T, Kiuchi T, Okuhara T, Kizawa Y. Health Care Providers' Knowledge, Confidence, Difficulties, and Practices after Completing a Communication Skills Training Program for Advance Care Planning Discussion in Japan. Annals of Palliative Medicine. 2021; 10(7):7225-7235.
7. Shirabe R, Okuhara T, Yokota R, Okada H, Goto E, Kiuchib T. Changes in Anxiety and Stress Among Pregnant Women During the COVID-19 Pandemic: Content Analysis of a Japanese Social Question-and-Answer Website. JMIR Pediatrics and Parenting 2021;4(3):e27733.

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)

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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 four courses in the master degree program for public health, and seven 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 sociopolitical 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 change in social problems through advocacy, social business, and community management, through 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 work places. 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 ills, 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, chronic illness experience, and social stigma.
   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 an ongoing research of socioeconomic status and health/functions among elderly population 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) is 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 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.

The department kept a close relationship with the study project of a large cohort for social epidemiology in gerontology, called Japan Gerontological Evaluation Study (JAGES) that covers more than 30 municipalities and approximately 200,000 participating old people in the community. The project purports to reveal social relationship and its impact on health in later life.

Dr. Takagi, in collaboration with Niigata University, is preparing for a 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. Kamada, in collaboration with Tokyo Medical University, Harvard University, and Unnan 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.

Prof. Hashimoto started a joint project with the Tokyo Metropolitan Government on the information management in the field of welfare programs to tackle child maltreatment. The project purports to develop standardized information systems and support skills development for effective case recording to enhance inter-sector communication and improve the quality of welfare activities.

Other Social activities

The department continued to join the public health center to support efficient information management during the pandemic surge of COVID19 in Adachi Ward in Metropolitan Tokyo.

Publications

Peer reviewed journals

1. Kamada M, Hayashi H, Shiba K, Taguri M, Kondo N, Lee IM, Kawachi I. Large-scale fandom-based gamification intervention to increase physical activity: a quasi-experimental study. Medicine & Science in Sports & Exercise. 54(1):181-188, 2022. DOI: 10.1249/MSS.0000000000002770
2. Bauman AE, Kamada M, Reis RS, Troiano RP, Ding D, Milton K, Murphy N, Hallal PC. An evidence-based assessment of the impact of the Olympic Games on population levels of physical activity. Lancet. 398(10298), 456-464, 2021. doi: 10.1016/S0140-6736(21)01165-X.
3. Tobías A, Casals M, Saez M, Kamada M, Kim Y. Impacts of ambient temperature and seasonal changes on sports injuries in Madrid, Spain: a time-series regression analysis. BMJ Open Sport Exerc Med. 7(4):e001205, 2021. DOI: 10.1136/bmjsem-2021-001205.
4. Sasaki N, Obikane E, Vedanthan R, Imamura K, Cuijpers P, Shimazu T, Kamada M, Kawakami N, Nishi D. Implementation Outcome Scales for Digital Mental Health (iOSDMH): scale development and cross-sectional study. JMIR Formative Research. 5(11):e24332, 2021. doi:10.2196/24332
5. Abe T, Okuyama K, Hamano T, Kamada M, Isomura M, Nabika T, Miyazaki R. Association between hilliness and walking speed in community-dwelling older Japanese adults: A cross-sectional study. Arch Gerontol Geriatr. 97:104510, 2021. doi:10.1016/j.archger.2021.104510
6. Saito Y, Tanaka A, Tajima T, Ito T, Aihara Y, Nakano K, Kamada M, Inoue S, Miyachi M, Lee IM, Oguma Y. A community-wide intervention to promote physical activity: A five-year quasi-experimental study. Prev Med. 150:106708, 2021. doi:10.1016/j.ypmed.2021.106708

7. Shiba K, Torres JM, Daoud A, Inoue K, Kanamori S, Tsuji T, Kamada M, Kondo K, Kawachi I. Estimating the impact of sustained social participation on depressive symptoms in older adults. Epidemiology. 32(6):886-895, 2021. doi: 10.1097/EDE.0000000000001395
8. Amagasa S, et al. Smartphone and wearable device use in physical activity evaluation in healthcare scienc. Jpn J Public Health. 68(9): 585-596, 2021.
9. Masuda R, Lanier P, Peisner-Feinberg E, Hashimoto H. A Quasi-Experimental Study of the Effects of Pre-Kindergarten Education on Pediatric Asthma. Int J Environ Res Public Health. 2021 Oct 5;18(19):10461. doi: 10.3390/ijerph181910461.
10. Kim H, Jeon B, Doetter L, Tamiya N, Hashimoto H. (2021). Same same but different? Comparing institutional performance in the long-term care systems of Japan and South Korea. Social Policy & Administration. 10.1111/spol.12761.
11. Kanamori, M., Hanazato, M., Takagi, D., Kondo, K., Ojima, T., Amemiya, A., & Kondo, N. (2021). Differences in depressive symptoms by rurality in Japan: A cross-sectional multilevel study using different aggregation units of municipalities and neighborhoods (JAGES). International Journal of Health Geographies, 20:42.
12. Nishio, M., Takagi, D., Shinozaki, T., & Kondo, N. (2021). Community social networks, individual social participation and dietary behavior among older Japanese adults: Examining mediation using nonlinear structural equation models for three-wave longitudinal data. Preventive Medicine, 149:106613.
13. Sasaki, Y., Shobugawa., Y, Nozaki., I, Takagi, D., Nagamine, Y., Funato, M., Chihara, Y., Shirakura, Y., Lwin, K. T., Zin, P. E., Bo, T. Z., Sone, T., Win, H. H. (2021). Rural-urban differences in the factors affecting depressive symptoms among older adults of two regions in Myanmar. International Journal of Environmental Research and Public Health, 18:2818.
14. Sasaki, Y., Shobugawa, Y., Nozaki, I., Takagi, D., Nagamine, Y., Funato, M., Chihara, Y., Shirakura, Y., Lwin, K. T., Zin, P. E., Bo, T. Z., Sone, T., Win, H. H. (2021). Association between depressive symptoms and objective/subjective socioeconomic status among older adults of two regions in Myanmar. PloS ONE, 16: e0245489.

Book chapter

1. Takagi D. (2021).Social network and social contagion. In Inada Y. eds. Human relationship with Social capital view (pp. 64-80). Nippon Hyoronsha.

School of Public Health

3. Health Services Sciences

Department of Clinical Information Engineering

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Assistant professor

Ayako Kohyama-Koganeya, Ph.D.

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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 bio-chemistry 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 that focus on biomedical 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 research 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 WG, Kohyama-Koganeya A, Saito T, Oyama H. Effect of a Contact-based Educational Intervention Using Virtual Reality on the Public Stigma of Depression: A Randomized Controlled Pilot Study. JMIR Form Res (forthcoming). doi:10.2196/28072
2. Lem WG, Kohyama-Koganeya A, Saito T, Oyama H. Virtual reality-based anti-stigma (VRAS) application for depression stigma education. JMVR Vol 18. No.1, 2021.
3. Nagayo, Y., Saito, T., & Oyama, H. (2021). A Novel Suture Training System for Open Surgery Replicating Procedures Performed by Experts Using Augmented Reality. Journal of Medical Systems, 45(5), 1-9.
4. Nomura, S., Kin, T., Kunimatsu, A., Shojima, M., Watanebe, Y., Suzuki, Y., …, Oyama, H. & Saito, N. (2021). Registration Method Between Phase-Contrast Magnetic Resonance Angiography and Time-of-Flight Magnetic Resonance Angiography — A Preliminary Study. Journal of Medical Imaging and Health Informatics, 11(1), 33-39.
5. Koike, T., Kin, T., Tanaka, S., Sato, K., Uchida, T., Takeda, Y., …, Oyama, H. & Saito, N. (2021). Development of a New Image-Guided Neuronavigation System: Mixed-Reality Projection Mapping Is Accurate and Feasible. Operative Neurosurgery.
6. Koike, T., Kin, T., Tanaka, S., Takeda, Y., Uchikawa, H., Shiode, T., … Oyama, H. & Saito, N. (2021). Development of Innovative Neurosurgical Operation Support Method Using Mixed-Reality Computer Graphics. World neurosurgery: X, 11, 100102.

Department of Global Environmental Health

Associate Professor

Yoonhee Kim, Ph.D.

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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, and takes 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 under 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 also 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 weekly conference call with multiple schools/institutes* to read and discuss articles in environmental epidemiology.

*Seoul National University, Korea Advanced Institute of Science & Technology (KAIST), National Institute for Environmental Studies, University of Tsukuba, Kyoto University, and Nagasaki University

GEH R Seminar

Every other Tuesday, 11:00-12:30

Graduate students present fundamental knowledge and skills of R language and its applications that they learned from R textbooks and/or research articles in environmental epidemiology. Sharing the basic and advanced methodologies and discussion help students develop their capacity to implement research projects.

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 Collaborative Research Network
2. Health risk assessment of climate change and air pollution in northeast Asian countries
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

Publications

1. Tobías A, Casals M, Saez M, Kamada M, Kim Y. Impacts of ambient temperature and seasonal changes on sports injuries in Madrid, Spain: a time-series regression analysis. BMJ Open Sport & Exercise Medicine 2021:7:e001205.
2. Kim Y, Park EH, Ng CFS, Chung Y, Hashimoto K, Tashiro K, Hasunuma H, Doi M, Tamura K, Moriuchi H, Nishiwaki Y, Kim H, Yi S-M, Kim H, Hashizume M. Respiratory function declines in children with asthma associated with chemical species of fine particulate matter ($PM_{2.5}$) in Nagasaki, Japan. Environ Health 2021:20:110.
3. Tobías A, Hashizume M, Honda Y, Sera F, Ng CFS, Kim Y, Roye D, Chung Y, Dang TN, Kim H, Lee W, Íñiguez C, Vicedo-Cabrera A, et al. Geographical Variations of the Minimum Mortality Temperature at a Global Scale: A Multicountry Study. Environmental Epidemiology 2021:5:e169.
4. Madaniyazi L, Chung Y, Kim Y, Tobias A, Ng CFS, Seposo X, Guo Y, Honda Y, Gasparrini A, Armstrong B, Hashizume M. Seasonality of mortality under a changing climate: a time-series analysis of mortality in Japan between 1972 and 2015. Environ Health Prev Med. 2021:3:26:69.
5. Lee W, Ebi KL, Kim Y, Hashizume M, Honda Y, Hashimoto H, Choi HM, Choi M, Kim H. Heat-mortality risk and the population concentration of metropolitan areas in Japan: a nationwide time-series study. International Journal of Epidemiology 2021:50:602–612.
6. Yu J, Park J, Choi T, Hashizume M, Kim Y, Honda Y, Chung Y. Nonparametric Bayesian functional meta-regression: applications in environmental epidemiology. Journal of Agricultural, Biological, and Environmental Statistics 2021:26: 45–70.

Endowed Department

Department of Artificial Intelligence in Healthcare

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Emiko Shinohara, Ph.D.

Project Research Associate

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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, to explore the form of new medical services while promoting the development of underlying technologies, such as, ICT and AI. The objective has been to contribute to human resource development by forming a support base for researchers involved in this field, and to develop joint research beyond the boundaries of faculties and universities to contribute to the development of medical care.

Teaching activities

We have promoted activities to train researchers as well as students in this area inside and outside the university. In 2021, 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 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.

Research to support renal pathological diagnosis

With the development of deep neural networks, AI development research in medical imaging has become widespread. To date, we have received a Health Labor Sciences Research Grant. Under multi-institutional collaboration, we have been developing technology to detect minute glomeruli from digital pathological slides (whole slide images) along with research to classify the pathological findings of the detected glomeruli. In 2020, we further developed this research and proceeded with the evaluation of the interoperability of the developed technology across multiple facilities to quantify the lesion area of the glomerulus. Precise quantification of lesion area may lead to prediction of renal function prognosis based on pathological images and new interpretation of pathological findings.

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. Kawazoe Y, Shibata D, Shinohara E, Aramaki E, Ohe K. A clinical specific BERT developed using a huge Japanese clinical text corpus. PLoS One. 2021 Nov 9;16(11): e0259763.
2. Seki T, Kawazoe Y, Ohe K. Machine learning-based prediction of in-hospital mortality using admission laboratory data: A retrospective, single-site study using electronic health record data. PLoS ONE. 2021;16(2): e0246640.
3. Ma X, Imai T, Shinohara E, Kasai S, Kato K, Kagawa R, Ohe K. EHR2CCAS: A framework for mapping EHR to disease knowledge presenting causal chain of disorders – chronic kidney disease example. J Biomed Inform. 2021 Mar; 115:103692.
4. Ishii, Futoshi, Reiko Hayashi, Emiko Shinohara, Motomi Beppu. Application of Network Analysis to Multiple Causes of Death Data in Japan. The 29th International Population Conference (IPC2021), International Union for the Scientific Study of Population (IUSSP), Dec. 9, 2021.

Health Economy and Society Policy

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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. Shohei Okazaki, Kei Shibuya, Yuhei Miyasaka, Hidemasa Kawamura, Tomoyuki Takura, Tatsuya Ohno. Cost-Effectiveness of Carbon-Ion Radiotherapy versus Stereotactic Body Radiotherapy for Non-Small Cell Lung Cancer. Cancer Science. 2012;113(2):674-683. doi: 10.1111/cas.15216.
2. Tomoyuki Takura, Keiko Goto, Asao Honda. Development of a predictive model for integrated medical and long-term care resource consumption based on health behaviour: application of health-care big data of patients with circulatory diseases. BMC medicine. 2021;19(1):15. doi: 10.1186/s12916-020-01874-6.
3. Tomoyuki Takura, Akira Yuasa, Naohiro Yonemot, Sven Demiya, Hiroyuki Matsuda, Nozomi Ebata, Koichi Fujii, Muneaki Ishijima. Cost-effectiveness analysis of the treatment strategies with or without opioid medications in surgery-eligible patients with osteoarthritis in Japan. Pharmaco Economics - Open. 2021; 6(1): 33-45. doi: 10. 1007/s416 69-021-00292-5.
4. Tomoyuki Takura, Study Group: Research on Appropriate Medical Treatment Prices for Foreigners Visiting Japan. Preliminary Examination of an Appropriate Price Calculation Method and Medical Treatment Costs for Foreign Visitors in Japan. Int. J. Environ. Res. Public Health. 2021; 18(11):5837. doi: 10.3390/ijerph18115837.
5. Tomoyuki Takura, Hiroyoshi Yokoi, Nobuhiro Tanaka, Naoya Matsumoto, Eri Yoshida, Tomoaki Nakata, J-CONCIOUS Investigators. Health economics-based verification of functional myocardial ischemia evaluation of stable coronary artery disease in Japan: A long-term longitudinal study using propensity score matching. J Nucl Cardiol. 2021. In press. doi: 10.1007/s12350-020-02502-9.
6. Kaname Ueda, Tomoyuki Takura, Shinji Fujikoshi, Juliana Meyers, Saurabh P Nagar, Hiroyuki Enomoto. Long-Term Pain Management and Health Care Resource Use Among an Employed Population in Japan with Knee Osteoarthritis Combined with Low Back Pain. Pain Med. 2021; 22(12):3041-3050. doi: 10.1093/pm/pnaa424.
7. Tomoyuki Takura. The Economic Aspects of Medical Big Data. CANCER SCIENCE. 2021; 112(11):147-147.
8. Shiro Imagama, Hideki Murakami, Takashi Kaito, Yukihiro Matsuyama, Toshihiko Yamashita, Mamoru Kawakami, Kazuhisa Takahashi, Munehito Yoshida, Seiji Ohtori, Toshihiko Taguchi, Hirotaka Haro, Hiroshi Taneichi, Masashi Yamazaki, Gen Inoue, Kotaro Nishida, Hiroshi Yamada, Daijiro Kabata, Ayumi Shintani, Motoki Iwasaki, Manabu Ito, Naohisa Miyakoshi, Kazuo Yonenobu, Tomoyuki Takura, Joji Mochida, Project Committee of the Japanese Society for Spine Surgery and Related Research (JSSR). Impact of background factors on outcomes of pharmacological therapy for chronic low back pain: A nationwide multicenter prospective study. J Orthop Sci. 2021 ;26(1):92-102. doi: 10.1016/j.jos.2020.02.003.
9. Tomoyuki Takura. Adherence improves long-term prognosis and medical costs in Japan. GaBi – online. 2021; 19(2). https://gabionline.net/generics/research/Adherence-improves-long-term-prognosis-and-medical-costs-in-Japan. (Accessed August 28, 2022)
10. Gen Inoue, Takashi Kaito, Yukihiro Matsuyama, Toshihiko Yamashita, Mamoru Kawakami, Kazuhisa Takahashi, Munehito Yoshida, Shiro Imagama, Seiji Ohtori, Toshihiko Taguchi, Hirotaka Haro, Hiroshi Taneichi, Masashi Yamazaki, Kotaro Nishida, Hiroshi Yamada, Daijiro Kabata, Ayumi Shintani, Motoki Iwasaki, Manabu Ito, Naohisa Miyakoshi, Hideki Murakami, Kazuo Yonenobu, Tomoyuki Takura, Joji Mochida. Comparison of the Effectiveness of Pharmacological Treatments for Patients with

Chronic Low Back Pain: A Nationwide, Multicenter Study in Japan. 2021;5(4):252-263. doi: 10.22603/ssrr.2020-0083.

Department of medical research and the management of musculoskeletal pain

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Introduction and Organization

The department of medical research and the management of musculoskeletal pain was established at the 22nd Century Medical and Research Centre thanks to donations from ippon Zoki Pharmaceutical Co., Ltd., AYUMI Pharmaceutical Corporation, ONO PHARMACEUTICAL CO., LTD., Chugai Pharmaceutical Co., Ltd., SOMPO Holdings, Inc., NuVasive Japan Co., Ltd., Promotion of Practical Use of AI Medical Diagnosis Support Equipment, MS&AD InterRisk Research & Consulting, Inc, Inotech Co., Ltd., The Association for Preventive Medicine in Japan, DeNA Co., Ltd., Ibuki LLC. The department is a collaboration among the Department of Orthopaedics, the Department of Rehabilitation Medicine. Currently, our aims are to design an algorithm for diagnosing and treating most types of musculoskeletal pain that do not have established treatment guidelines and to elucidate evidence for the possibility of developing causal therapies.

In the “Comprehensive Survey of Living Conditions” and the “Survey on the Status of Occurrence of Diseases at Work,” which were published by the Health, Labour, and Welfare Ministry, the issues affecting the locomotive apparatus over the years, particularly low back pain and joint pain, have been ranked as the top complaints among citizens and as a cause of absence from work. Musculoskeletal pain, mainly low back pain and joint pain, is an issue with a high complaint rate that causes tremendous social loss.

The course on medical research and the management of musculoskeletal pain was made available to provide more knowledge on highly prevalent musculoskeletal pain and to become a core programme in leading multidisciplinary clinical research.

To achieve these goals, we will closely collaborate with the Department of Orthopaedics, Department of Spinal Surgery, Department of Rehabilitation. On the basis of an extensive epidemiological survey, we will identify risk factors that contribute to determining the therapeutic strategy for treating musculoskeletal pain as well as the prognosis. In addition, on the basis of these determined risk factors, we will develop and propose diagnostic tools/algorithms as well as prevention and treatment programmes. Then we will collect and analyse clinical data and systematise the diagnosis, prevention, and treatment of chronic pain – mainly musculoskeletal pain.

Research activities

We will explore the risk factors that contribute to determining the therapeutic strategy for treating musculoskeletal pain and the prognosis.

Prospects for future research

1) Systematization of chronic pain, mainly motor organ pain (collection and analysis of clinical data)

A manual that can realize back pain prevention in the field of industrial health, treatment and work balance support for workers who have diseases that cause motor pain, such as cancer patients, support for balancing chronic pain and work/reducing health costs.

2) Development of diagnostic tools and treatment programs for musculoskeletal pain

Development of back pain preventive exercise, development of sensor for presenting posture to prevent back pain, development of quantitative evaluation system for knee oseteoarthritis X-ray based on a large database, clinical information, and medical images of musculoskeletal diseases. Developed a system that predicts sarcopenia and muscle weakness with high accuracy by using medical equipment (non-invasive and simple ultrasound and artificial intelligence), spinal canal and paraspinal muscle of lumbar spine for quantitative evaluation of fatty degeneration in humans (joint research with Dr. Jeremy Fairbank, University of Oxford).

3) Fostering clinicians who are familiar with musculoskeletal pain assessment and treatment, and enlightening the general public with evidence-based knowledge about musculoskeletal pain

References

1. Okada S, Oka H, Iwasaki H, Tsutsui S, Yamada H. New diagnostic support tool for lumbosacral foraminal stenosis using radiographs of the lumbar spine. J Clin Neurosci. 2022 Feb;96:8-11. doi: 10.1016/j.jocn.2021.12.009. Epub 2021 Dec 22. PMID: 34953440.
2. Yamada K, Fujii T, Kubota Y, Wakaizumi K, Oka H, Matsudaira KO. Negative effect of anger on chronic pain intensity is modified by multiple mood states other than anger: A large population-based cross-sectional study in Japan. Mod Rheumatol. 2021 Aug 12: roab035. doi: 10.1093/mr/roab035. Epub ahead of print. PMID: 34910207.
3. Horii C, Iidaka T, Muraki S, Oka H, Asai Y, Tsutsui S, Hashizume H, Yamada H, Yoshida M, Kawaguchi H, Nakamura K, Akune T, Oshima Y, Tanaka S, Yoshimura N. The cumulative incidence of and risk factors for morphometric severe vertebral fractures in Japanese men and women: the ROAD study third and fourth surveys. Osteoporos Int. 2022 Apr;33(4):889-899. doi: 10.1007/s00198-021-06143-7. Epub 2021 Nov 19. PMID: 34797391.
4. Teraguchi M, Hashizume H, Oka H, Cheung JPY, Samartzis D, Tamai H, Muraki S, Akune T, Tanaka S, Yoshida M, Yoshimura N, Yamada H. Detailed Subphenotyping of Lumbar Modic Changes and Their Association with Low Back Pain in a Large Population-Based Study: The Wakayama Spine Study. Pain Ther. 2022 Mar; 11(1):57-71. doi: 10.1007/s40122-021-00337-x. Epub 2021 Nov 15. PMID: 34782999; PMCID: PMC8861214.
5. Hira K, Nagata K, Hashizume H, Asai Y, Oka H, Tsutsui S, Takami M, Iwasaki H, Muraki S, Akune T, Iidaka T, Kawaguchi H, Nakamura K, Yoshida M, Tanaka S, Yoshimura N, Yamada H. Relationship of sagittal spinal alignment with low back pain and physical performance in the general population. Sci Rep. 2021 Oct 18; 11(1):20604. doi: 10.1038/s41598-021-00116-w. PMID: 34663811; PMCID: PMC8523667.
6. Anan T, Kajiki S, Oka H, Fujii T, Kawamata K, Mori K, Matsudaira K. Effects of an Artificial Intelligence-Assisted Health Program on Workers With Neck/Shoulder Pain/Stiffness and Low Back Pain: Randomized Controlled Trial. JMIR Mhealth Uhealth. 2021 Sep 24;9(9):e27535. doi: 10.2196/27535. PMID: 34559054; PMCID: PMC 8501409.
7. Nishizawa A; PO, Katsuhira J, Watanabe M, Oka H, Matsudaira K. A simple method for estimating the intervertebral disc compressive force based on the posture analysis of community-dwelling older adults. J Phys Ther Sci. 2021 May;33(5): 423-428. doi: 10.1589/jpts.33.423. Epub 2021 May 15. PMID: 34083882; PMCID: PMC 8165360.
8. Ishii K, Oka H, Honda Y, Oguro D, Konno Y, Kumeta K, Nishihara S, Matsuyama H, Kaneko I,

Takeuchi Y, Watanabe Y, Kawano H, Ogata N. Accuracy and reliability of a smartphone application for measuring the knee joint angle. J Phys Ther Sci. 2021 May;33(5):417-422. doi: 10.1589/jpts.33.417. Epub 2021 May 15. PMID: 34083881; PMCID: PMC8165359.

9. Yoshimoto T, Fujii T, Oka H, Kasahara S, Kawamata K, Matsudaira K. Pain Status and Its Association with Physical Activity, Psychological Stress, and Telework among Japanese Workers with Pain during the COVID-19 Pandemic. Int J Environ Res Public Health. 2021 May 24;18(11): 5595. doi: 10.3390/ijerph18115595. PMID: 34073863; PMCID: PMC8197253.
10. Otsuka Y, Iidaka T, Horii C, Muraki S, Oka H, Nakamura K, Izumo T, Rogi T, Shibata H, Tanaka S, Yoshimura N. Dietary Intake of Vitamin E and Fats Associated with Sarcopenia in Community-Dwelling Older Japanese People: A Cross-Sectional Study from the Fifth Survey of the ROAD Study. Nutrients. 2021 May 20;13(5):1730. doi: 10.3390/nu13051730. PMID: 34065253; PMCID: PMC8161000.
11. Kasahara S, Niwa SI, Matsudaira K, Sato N, Oka H, Fujii T, Konno SI, Kikuchi SI, Yamada Y. High Attention-Deficit/Hyperactivity Disorder Scale Scores Among Patients with Persistent Chronic Nonspecific Low Back Pain. Pain Physician. 2021 May;24(3):E299-E307. PMID: 33988951.
12. Nagata K, Nakamoto H, Kato S, Takeshita Y, Kawamura N, Ono T, Higashikawa A, Fukushima M, Azuma S, Hara N, Oka H, Matsudaira K, Tanaka S, Oshima Y. Minimum clinically important change for outcome scores among patients aged 75 or over undergoing lumbar spine surgery. Eur Spine J. 2021 May;30(5):1226-1234. doi: 10.1007/s00586-021-06815-2. Epub 2021 Mar 20. PMID: 33743055.
13. Taniguchi T, Harada T, Iidaka T, Hashizume H, Taniguchi W, Oka H, Asai Y, Muraki S, Akune T, Nakamura K, Kawaguchi H, Yoshida M, Tanaka S, Yamada H, Yoshimura N. Prevalence and associated factors of pistol grip deformity in Japanese local residents. Sci Rep. 2021 Mar 16; 11(1):6025. doi: 10.1038/s41598-021-85521-x. PMID: 33727622; PMCID: PMC7966377.
14. Tonosu J, Oka H, Watanabe K, Abe H, Higashikawa A, Kawai T, Yamada K, Nakarai H, Tanaka S, Matsudaira K. Characteristics of the spinopelvic parameters of patients with sacroiliac joint pain. Sci Rep. 2021 Mar 4;11(1):5189. doi: 10.1038/s41598-021-84737-1. PMID: 33664386; PMCID: PMC7970840.
15. 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. 2021 Jan 28:2192568221989655. doi: 10.1177/2192568221989655. Epub ahead of print. PMID: 33504203.
16. Inanami H, Iwai H, Kato S, Takano Y, Yuzawa Y, Yanagisawa K, Kaneko T, Segawa T, Matsudaira K, Oka H, Oshina M, Fukusima M, Saiki F, Oshima Y. Partial Resection of Spinous Process for the Elderly Patients with Thoraco-Lumbar Kyphosis: Technical Report. Medicina (Kaunas). 2021 Jan 21;57(2):87. doi: 10.3390/medicina 57020087. PMID: 33494142; PMCID: PMC 7909842.
17. Kozaki T, Hashizume H, Nishiyama D, Iwasaki H, Tsutsui S, Takami M, Yukawa Y, Minamide A, Taniguchi T, Nagata K, Fukui D, Tamai H, Taiji R, Murata S, Oka H, Yamada H. Adjacent segment disease on hip joint as a complication of spinal fusion surgery including sacroiliac joint fixation. Eur Spine J. 2021 May;30(5):1314-1319. doi: 10.1007/s00586-020-06700-4. Epub 2021 Jan 3. PMID: 33389138.
18. Oshima Y, Nagata K, Nakamoto H, Sakamoto R, Takeshita Y, Ohtomo N, Kawamura N, Iizuka M, Ono T, Nakajima K, Higashikawa A, Yoshimoto T, Fujii T, Tanaka S, Oka H, Matsudaira K. Validity of the Japanese core outcome measures index (COMI)-neck for cervical spine surgery: a prospective cohort study. Eur Spine J. 2021 Feb; 30(2):402-409. doi: 10.1007/s00586-020-06657-4. Epub 2020 Nov 19. PMID: 33211189.
19. Mera Y, Teraguchi M, Hashizume H, Oka H, Muraki S, Akune T, Kawaguchi H, Nakamura K,

Tamai H, Tanaka S, Yoshida M, Yoshimura N, Yamada H. Association between types of Modic changes in the lumbar region and low back pain in a large cohort: the Wakayama spine study. Eur Spine J. 2021 Apr;30(4):1011-1017. doi: 10.1007/s00586-020-06618-x. Epub 2020 Oct 9. PMID: 33037486.

20. Jinnouchi H, Matsudaira K, Kitamura A, Kakihana H, Oka H, Hayama-Terada M, Yamagishi K, Kiyama M, Iso H; CIRCS Investigators. Effects of brief self- exercise education on the management of chronic low back pain: A community- based, randomized, parallel-group pragmatic trial. Mod Rheumatol. 2021 Jul;31(4):890-898. doi: 10.1080/14397595.2020.1823603. Epub 2020 Oct 9. PMID: 32930621.
21. Ono K, Ohashi S, Oka H, Kadono Y, Yasui T, Matsumoto T, Omata Y, Tanaka S. Evaluations of daily teriparatide using finite-element analysis over 12 months in rheumatoid arthritis patients. J Bone Miner Metab. 2021 Mar;39(2):270-277. doi: 10.1007/s00774-020-01146-6. Epub 2020 Sep 4. PMID: 32886175.

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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. Osteo-immunology 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 osteo-immunology in May 2016. and now is supported by AYUMI Pharmaceutical Corporation, Chugai Pharmaceutical, MIKI HOUSE and Noevir. We aim to understand the mechanisms underlying the patho-genesis of various skeletal and immune diseases, and to provide the molecular basis for novel drug discovery in the field. Project Assistant Professor Terashima left on September 30, 2021.

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 patho-genesis of the diseases, and provide the molecular basis for novel therapeutic strategies. Our achieve-ment 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.

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-prodcing 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 methyl-transferase 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 (γc) 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 γc 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.

References

1. Mikhail M Kostik, Maria A Makhova, Alexei S Maletin, Shamai M Magomedova, Lybov S Sorokina, Masayuki Tsukasaki, Kazuo Okamoto, Hiroshi Takayanagi, Dmitriy S Vasiliev, Darya I Kozlova, Alexander Yu Mushkin. Cytokine profile in patients with chronic non-bacterial osteomyelitis, juvenile idiopathic arthritis, and insulin-dependent diabetes mellitus. *Cytokine*, 143: 155521, 2021
2. Komatsu N, Win S, Yan M, Huynh N C-N, Sawa S, Tsukasaki M, Terashima A, Pluemsakunthai W, Kollias G, Nakashima T, Takayanagi H. Plasma cells promote osteoclastogenesis and periarticular bone loss in autoimmune arthritis. *J Clin Invest*. 131: e143060, 2021
3. Kazuo Okamoto. Role of RANKL in cancer development and metastasis. *Journal of Bone and Mineral Metabolism*, 39: 71-81, 2021

Department of Computational Diagnostic Radiology and Preventive Medicine

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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) Aoyama G, Zhao L, Zhao S, Xue X, Zhong Y, Yamauchi H, Tsukihara H, Maeda E, et al. Automatic Aortic Valve Cusps Segmentation from CT Images Based on the Cascading Multiple Deep Neural Networks. Journal of Imaging 2022;8(1):11.
2) Fujiwara T, Takeda N, Hara H, Ishii S, Numata G, Tokiwa H, et al. Three-Dimensional Visualization of Hypoxia-Induced Pulmonary Vascular Remodeling in Mice. Circulation 2021;144(17): 1452-1455.
3) Goo HW, Siripornpitak S, Chen SJ, Lilyasari O, Zhong YM, Latiff HA, Maeda E, et al. Pediatric Cardiothoracic CT Guideline Provided by the Asian Society of Cardiovascular Imaging Congenital Heart Disease Study Group: Part 2. Contemporary Clinical Applications. Korean J Radiol 2021 Aug;22(8):1397-1415.
4) Goto K, Minatsuki S, Fujita K, Takeda N, Hatano M, Komuro I. Two Siblings With Peripheral Pulmonary Arterial Stenosis: Pulmonary Angiography of Advanced and Early Stages. Chest 2022;161(2):e75-e80.
5) Han C, Rundo L, Murao K, Noguchi T, Shimahara Y, Milacski ZÁ, Koshino S, et al. MADGAN: Unsupervised medical anomaly detection GAN using multiple adjacent brain MRI slice reconstruction. BMC Bioinformatics 2021;22(2):1-20.
6) Hatano M, Jimba T, Fujiwara T, Tsuji M, Bujo C, Ishida J, et al. Late-onset right ventricular failure after continuous-flow left ventricular assist device implantation: case presentation and review of the literature. J Cardiol 2021.
7) Hiroyuki KMT, Masaatsu A, Cristiano B, Rosa C, Jon G, Naoto H, et al. First results of undersea muography with the Tokyo-Bay Seafloor Hyper-Kilometric Submarine Deep Detector. Scientific reports 2021;11(1):1-13.
8) Ishizuka M, Harada M, Nomura S, Ko T, Ikeda Y, Guo J, Bujo S, Yanagisawa-Murakami H, Satoho M, Yamada S, Kumaga H, Motozawa Y, Hara H, Fujiwara T, et al. Author Correction: CXCR7 ameliorates myocardial infarction as a β-arrestin-biased receptor. Scientific Reports 2021;11(1): 1-3.
9) Kamio S, Kubo T, Koshino S, Abe O. Successful transcatheter arterial embolization for pseudo-aneurysm of the deep femoral artery in a patient with presumptive ACTA2-related vasculopathy. Radiology Case Reports 2021;16(12):3652-3654.
10) Ko T, Nomura S, Fujita K, Yamada S, Zhang B, Hatsuse S, et al. Cardiac Fibroblasts Are Critically Involved in the Development of Heart Failure by Inducing Cardiomyocyte Senescence. Circulation 2021;144(Suppl_1):A9339-A9339.
11) Miki S, Nakao T, Nomura Y, Okimoto N, Nyunoya K, Nakamura Y, et al. Computer-aided

detection of cerebral aneurysms with magnetic resonance angiography: usefulness of volume rendering to display lesion candidates. Japanese Journal of Radiology 2021;39(7):652-658.

12) Miki S, Nomura Y, Hayashi N, Hanaoka S, Maeda E, Yoshikawa T, et al. Prospective study of spatial distribution of missed lung nodules by readers in CT lung screening using computer-assisted detection. Acad Radiol 2021;28(5):647-654.
13) Nakamura Y, Hanaoka S, Nomura Y, Nakao T, Miki S, Watadani T, et al. Automatic detection of actionable radiology reports using bidirectional encoder representations from transformers. BMC Medical Informatics and Decision Making 2021; 21(1):1-19.
14) Nakao T, Hanaoka S, Nomura Y, Murata M, Takenaga T, Miki S, et al. Unsupervised deep anomaly detection in chest radiographs. J Digital Imaging 2021;34(2):418-427.
15) 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.
16) Nomura Y, Hanaoka S, Nakao T, Hayashi N, Yoshikawa T, Miki S, et al. Performance changes due to differences in training data for cerebral aneurysm detection in head MR angiography images. Japanese Journal of Radiology 2021; 39(11):1039-1048.
17) Nomura Y, Hanaoka S, Takenaga T, Nakao T, Shibata H, Miki S, et al. Preliminary study of generalized semiautomatic segmentation for 3D voxel labeling of lesions based on deep learning. International Journal of Computer Assisted Radiology and Surgery 2021;16(11):1901-1913.
18) Shibata H, Hanaoka S, Nomura Y, Nakao T, Sato I, Sato D, et al. Versatile anomaly detection method for medical images with semi-supervised flow-based generative models. International Journal of Computer Assisted Radiology and Surgery 2021;16(12):2261-2267.
19) Shohji T, Kuriyama K, Yanano N, Maeda E, Katoh Y. Simple Method of Measuring SSDE for Head CT: Facilitating PRE-CT Scan Dose Calculation Using Specialized Head Scan Band. Radiat Prot Dosimet 2021;197(1):1-11.
20) Suto A, Ueha R, Ogura T, Maeda E, Tatebayashi M, Shimada D, et al. Swallowing computed tomography and virtual reality as novel imaging modalities for the diagnosis of clicking larynx: Two case reports. Auris Nasus Larynx 2022.
21) Suzuki T, Hirose K, Tabei F, Sugishita Y, Oka T, Ishii S, Fujiwara T, et al. An Autopsy Case of Pulmonary Veno-Occlusive Disease Complicated with Chronic Obstructive Pulmonary Disease and Severe Pulmonary Hypertension. International Heart Journal 2021;62(5):1186-1190.
22) Suzuki K, Otsuka Y, Nomura Y, Kumamaru KK, Kuwatsuru R, Aoki S. Development and Validation of a Modified Three-Dimensional U-Net Deep-Learning Model for Automated Detection of Lung Nodules on Chest CT Images From the Lung Image Database Consortium and Japanese Datasets. Acad Radiol 2022 February 2022;29:S11-S17.
23) Takenaga T, Hanaoka S, Nomura Y, Nakao T, Shibata H, Miki S, et al. Multichannel three-dimensional fully convolutional residual network-based focal liver lesion detection and classification in Gd-EOB-DTPA-enhanced MRI. International journal of computer assisted radiology and surgery 2021;16(9):1527-1536.
24) Yamada S, Ko T, Hatsuse S, Nomura S, Zhang B, Dai Z, Inoue S, Kubota M, Sawami K, Yamada T, Sassa T, Katagiri M, Fujita K. Spatiotemporal single-cell analysis reveals critical roles of mechano-sensing genes at the border zone in remodeling after myocardial infarction. 2021.
25) Yoshikawa M, Asaba K, Nakayama T. Causal effect of atrial fibrillation/flutter on chronic kidney disease: A bidirectional two-sample Mendelian randomization study. PloS one 2021; 16(12):e0261020.
26) Yoshikawa M, Asaba K. Educational attainment decreases the risk of COVID-19 severity in the European population: A two-sample Mendelian randomization study. Frontiers in public health 2021:510.
27) Yoshikawa M, Asaba K, Nakayama T. Estimating causal effects of atherogenic lipid-related traits on COVID-19 susceptibility

and severity using a two-sample Mendelian randomization approach. BMC medical genomics 2021;14(1):1-9.

Department of Cell Therapy in Regenerative Medicine

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Department Outline

The Department of Cell Therapy in Regenerative Medicine was established in 2021 to promote practical technologies for regenerative medicine, such as the development of mass culture of 3D mesenchymal stem cells (MSCs) and diagnostic imaging related to MSCs. MSCs are stem cells derived from the mesoderm, a type of somatic stem cells found *in vivo*, and can differentiate into bone, cartilage, and cardiomyocytes, etc. MSC culture methods are classified into two types: adherent cells (2D) and floating cells (3D), with 3D culture reported to be superior to 2D culture. Our department aims to develop technology for the mass culture of high-quality MSCs using Cellhesion®, a scaffold material developed by Nissan Chemical Corporation.

In recent years, cell quality evaluation has become necessary to ensure reproducibility, reliability, and accuracy in drug discovery research using cultured cells. MSCs are defined as cells expressing marker genes, such as CD105, CD73, CD90, etc. However, since it is impossible to determine the quality of MSCs, such as whether they are proliferating cells or not, even if these markers are expressed, it is important to have a method to evaluate the quality of MSCs. In addition, because the nature of MSCs vary among tissues of origin, donors, and other factors, even MSCs with a low number of passages may not proliferate and cannot be passaged. At present, it is left to the operator to decide at what stage to discontinue the culture. Our department will use Nikon Corporation's cell imaging technology to evaluate the cell quality during MSC 3D mass culture.

Research Content

Another important role of our department is to train many technicians who have mastered special techniques through research and development toward the practical application of high-quality 3D mass culture of MSCs and diagnostic imaging technology.

MSCs cultured with FCeM Cellhesion-MS, a scaffold material for MSC culture developed by Nissan Chemical for the regenerative medicine field, show approximately seven times more anti-inflammatory effects than conventional 2D cultured MSCs; and are expected to be applied for the treatment of various diseases. In FY2021, we measured the proliferative potential of 2D and 3D cultured MSCs and analyzed secreted factors related to angiogenesis and other factors. The cell proliferative capacity was higher in 2D than in 3D, but 3D cultures showed increased anti-inflammatory and angiogenic factors. The differentiation ability was observed under both culture conditions. In the future, the research and development will be carried out toward the practical application of cell imaging technology in 3D cell culture, and the effects of in vivo 3D cultured MSC transplantation will be evaluated.

Future Outlook

Based on the clinical research of 3D mass culture of MSCs and 3D-related diagnostic imaging technology, we would like to pursue the research and development of world-class and advanced regenerative medicine; and to engage in activities to globally deploy regenerative medicine technology originating from Japan.

References

1. Campagnoli C, Roberts IA, Kumar S, Bennett PR, Bellantuono I, Fisk NM. Identification of mesenchymal stem/progenitor cells in human first-trimester fetal blood, liver, and bone marrow. Blood. 2001 Oct; 98: 2396-2402.
2. Zuk PA, Zhu M, Ashjian P, Ugarte DA, Huang JI, Mizuno H, Alfonso ZC, Fraser JK, Benhaim P, Hedrick MH. Human adipose tissue is a source of multipotent stem cells. Mol Biol Cell. 2002 Dec; 13(12): 4279-4295
3. Olmar REI, Beroud J, Stoltz J-F, Menu P, Velot E, Decot V. Umbilical cord mesenchymal stem cells: The new gold standard for mesenchymal stem cell-based therapies? Tissue Eng Part B rev. 2014 Oct; 20(5): 523-544.
4. Anthony J Kanelidis, Courtney Premer, Juan Lopez, Wayne Balkan, Joshua M Hare. Route of Delivery Modulates the Efficacy of Mesenchymal Stem Cell Therapy for Myocardial Infarction: A Meta-Analysis of Preclinical Studies and Clinical Trials. Circ Res. 2017 Mar 31;120(7):1139-1150.
5. Li-Tzu Wang, Chiao-Hsuan Ting, Men-Luh Yen, Ko-Jiunn Liu, Huey-Kang Sytwu, Kenneth K Wu, B Linju Yen. Human mesenchymal stem cells (MSCs) for treatment towards immune- and inflammation-mediated diseases: review of current clinical trials. J Biomed Sci. 2016 Nov 4; 23(1):76.
6. Katsuda T, Kosaka N, Takeshita F, Ochiya T. The therapeutic potencial of mesenchymal stem cell-derived extracellular vesecles. Proteomics. 2013 May; 13 (10-11): 1637-1653.
7. Jun Zhang, Xiaowen Huang, Haijun Wang, Xiaoyan Liu, Tao Zhang, Yunchuan Wang, Dahai Hu. The challenges and promises of allogeneic mesenchymal stem cells for use as a cell-based therapy. Stem Cell Res Ther. 2015 Dec1; 6:234
8. Chen K, Wang D, Du WT, Han Z-B, Ren H, Chi Y, Yang SG, Zhu D, Bayard F, Han ZC. Human umbilical cord mesenchymal stem cells hUC-MSCs exert immunosuppressive activities through a PGE2-dependent mechanism. Clin Immunol. 2010 Mar.; 135: 448-458.
9. Zhou Y, Chan H, Li H, Wu Y. 3D culture increases pluripotent gene expression mesenchymal stem cells through relaxation of cytoskeleton tension. J Cell Mol Med. 2017 Jun; 21(6): 1073–1084.
10. Sethe S, Scutt A, Stolzing A. Aging of mesenchymal stem cells. Ageing Res Rev. 2006 Feb; 5(1): 91-116.
11. Ksiazek K. A comprehensive review on mesenchymal stem cell growth and senescence. Rejuvenation Res. 2009 Apr; 12 (2): 105-116.
12. Feng J, Yang S, Xu L, Tian H, Sun L, Tang X. Role of caspase-3 inhibitor in induced anoikis of mesenchymal stem cells in vitro. J Huazhong Univ Sci Technolog Med Sci. 2007 Apr;27(2): 183-5.
13. Eun Seo Kim, Katsuhiko Kida, Jongsoo Mok, Yeonwoo Seong, Seo Yeon Jo, Tatsuro Kanaki, Masato Horikawa, Kyung-Hee Kim, Tae Min Kim, Tae Sub Park, Joonghoon Park. Cellhesion VP enhances the immunomodulating potential of human mesenchymal stem cell-derived extracellular vesicles. Biomaterials. 2021 Apr; 271: 120742.
14. Rangasamy Jayakumar, Krishna Prasad Chennazhi, Sowmya Srinivasan, Shantikumar V Nair, Tetsuya Furuike, Hiroshi Tamura. Chitin scaffolds in tissue engineering. Int J Mol Sci. 2011;12(3):1876-87.
15. Hung-Jen Shao, Yu-Tsang Lee, Chiang-Sang Chen, Jyh-Horng Wang, Tai-Horng Young. Modulation of gene expression and collagen production of anterior cruciate ligament cells through cell shape changes on polycaprolactone/chitosan blends. Biomaterials. 2010 Jun;31(17):4695-705.
16. Guo-Shiang Huang, Lien-Guo Dai, Betty L Yen, Shan-hui Hsu. Spheroid formation of mesenchymal stem cells on chitosan and chitosan-hyaluronan membranes. Biomaterials. 2011 Oct; 32(29):6929-45.

17. Yuriy Petrenko, Eva Syková, Šárka Kubinová. The therapeutic potential of three-dimensional multipotent mesenchymal stromal cell spheroids. Stem Cell Res Ther. 2017 Apr 26;8(1):94.
18. Auletta JJ, Eid SK, Wuttisarnwattana P, Silva I, Metheny L, Keller MD, Guardia-Wolff R, Liu C, Wang F, Bowen T, Lee Z, Solchaga LA, Ganguly S, Tyler M, Wilson DL, Cooke KR. Human Mesenchymal Stromal Cells Attenuate Graft-Versus-Host Disease and Maintain Graft-Versus-Leukemia Activity Following Experimental Allogeneic Bone Marrow Transplantation. Stem Cells. 2015 Feb;33(2):601-14.
19. Kota DJ, Prabhakara KS, Toledano-Furman N, Bhattarai D, Chen Q, DiCarlo B, Smith P, Triolo F, Wenzel PL, Cox CS Jr, Olson SD. Prostaglandin E2 Indicates Therapeutic Efficacy of Mesenchymal Stem Cells in Experimental Traumatic Brain Injury. Stem Cells. 2017 May;35(5):1416-1430.
20. Song WJ, Li Q, Ryu MO, Ahn JO, Ha Bhang D, Chan Jung Y, Youn HY. TSG-6 Secreted by Human Adipose Tissue-derived Mesenchymal Stem Cells Ameliorates DSS-induced colitis by Inducing M2 Macrophage Polarization in Mice. Sci Rep. 2017 Jul 12;7(1):5187.
21. He Z, Hua J, Qian D, Gong J, Lin S, Xu C, Wei G, Meng H, Yang T, Zhou B, Song Z. Intravenous hMSCs Ameliorate Acute Pancreatitis in Mice via Secretion of Tumor Necrosis Factor-α Stimulated Gene/Protein 6. Sci Rep. 2016 Dec 5; 6:38438.
22. Lee RH, Pulin AA, Seo MJ, et al. Intravenous hMSCs improve myocardial infarction in mice because cells embolized in lung are activated to secrete the anti-inflammatory protein TSG-6. Cell Stem Cell. 2009, 5:54–63.
23. Usha Nekanti, Lipsa Mohanty, Parvathy Venugopal, Sudha Balasubramanian, Satish Totey, Malancha Ta. Optimization and scale-up of Wharton's jelly-derived mesenchymal stem cells for clinical applications. Stem Cell Res. 2010 Nov;5(3):244-54.
24. Roberta Tasso, Massimiliano Gaetani, Erica Molino, Angela Cattaneo, Massimiliano Monticone, Angela Bachi, Ranieri Cancedda. The role of bFGF on the ability of MSC to activate endogenous regenerative mechanisms in an ectopic bone formation model. Biomaterials. 2012 Mar;33(7): 2086-96.
25. Shiro Imagama, Ryoko Ogino, Shinya Ueno, Norihito Murayama, Naohiro Takemoto, Yoshiari Shimmyo, Taisuke Kadoshima, Shigeki Tamura, Mariko Kuroda, Yukihiro Matsuyama, Kenji Kadomatsu, Yasuhiro Morita, Teruyoshi Inoue, Naoki Ishiguro. Systemic treatment with a novel basic fibroblast growth factor mimics small-molecule compound boosts functional recovery after spinal cord injury. PLoS One. 2020 Jul 17; 15(7): e0236050.

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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 based upon contributions by Mr. Kazuteru Noguchi, JSH Co., Ltd., Japan Home Medical Care Inc., Towa Pharmaceutical Co. Ltd., Sawai Pharmaceutical Co. Ltd., and Ain Pharmaciez. Our department collaborates with Department of Geriatric Medicine. 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

Publications

1. Yamanaka T, Kidana K, Mizuki M, Akishita M. Comparison of regular home visits received by

older male and female patients from physicians. Geriatr Gerontol Int 2021;21:1148–1150.
2. Son BK, Akishita M, Yamanaka T, Toyoshima K, Tanaka T, Suthutvoravut U, Iijima K. Association between inflammatory potential of the diet and sarcopenia/its components in community-dwelling older Japanese men. Arch Gerontol Geriatr 2021;97:104481.
3. Yao N, Mutter JB, Berry JD, Yamanaka T, Mohess DT, Cornwell T. In Traditional Medicare, Modest Growth In The Home Care Workforce Largely Driven By Nurse Practitioners. Health Aff (Millwood) 2021;40(3):478-486.
4. Hirakawa Y, Hirahara S, Yamaguchi Y, Yamanaka T, Arai H, Miura H. Improving the quality of community primary palliative care in COPD: A qualitative study of health-care providers. Home Health Care Serv Q 2021;40(1):39-53.
5. Kikuchi K, Tatebe T, Sudo Y, Yokoyama M, Kidana K, Chiu YW, Takatori S, Arita M, Hori Y, Tomita T. GPR120 signaling controls amyloid-β degrading activity of matrix metalloproteinases. J Neurosci 2021;41(28):6173–85.

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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 devise (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: Amiya E. Link between hyperuricemia, renal dysfunction, and hypertension. J Clin Hypertens (Greenwich). 2021 Dec;23(12):2078-2079.

2: Bujo C, Amiya E, Hatano M, Ishida J, Tsuji M, Kakuda N, Narita K, Saito A, Yagi H, Ando M, Shimada S, Kimura M, Kinoshita O, Ono M, Komuro I. Long-Term renal function after implantation of continuous-flow left ventricular assist devices: A single center study. Int J Cardiol Heart Vasc. 2021 Nov 1;37:100907.

3: Itoh H, Amiya E, Narita K, Shimbo M, Taya M, Komuro I, Hasegawa T, Makita S, Kimura Y. Efficacy and Safety of Remote Cardiac Rehabilitation in the Recovery Phase of Cardiovascular Diseases: Protocol for a Multicenter, Non-randomized, Single-Arm, Interventional Trial. JMIR Res Protoc. 2021 Oct 4;10(10):e30725.

4: Ishiwata J, Daimon M, Nakanishi K, Sugimoto T, Kawata T, Shinozaki T, Nakao T, Hirokawa M, Sawada N, Yoshida Y, Amiya E, Hatano M, Morita H, Yatomi Y, Komuro I. Combined evaluation of right ventricular function using echocardiography in non-ischaemic dilated

cardiomyopathy. ESC Heart Fail. 2021 Oct;8(5): 3947-3956.
5: Narita K, Amiya E. Is branched-chain amino acid nutritional supplementation beneficial or detrimental in heart failure? World J Cardiol. 2021 26;13(6):163-169.
6: Narita K, Amiya E. Social and environmental risks as contributors to the clinical course of heart failure. Heart Fail Rev. 2022 Jul;27(4):1001-1016.
7: Dai Z, Uehara M, Amiya E, Hatano M, Komuro I. Acute cellular rejection after heart transplantation and its remission visualized by cardiac magnetic resonance. Eur Heart J Case Rep. 2021 Feb 28; 5(3):ytab085.
8: Kakuda N, Amiya E, Hatano M, Maki H, Bujo C, Tsuji M, Narita K, Fujita K, Ishida J, Ono M, Komuro I. Case Report: A Case of Acute Cellular Rejection Due to Atopic Dermatitis Exacerbation 3 Years After Heart Transplantation. Front Immunol. 2021 Feb 22;12:630051.
9: Tsuji M, Amiya E, Bujo C, Hara T, Saito A, Minatsuki S, Maki H, Ishida J, Hosoya Y, Hatano M, Imai H, Nemoto M, Kagami Y, Endo M, Kimura M, Ando M, Shimada S, Kinoshita O, Ono M, Komuro I. Carbon Monoxide Diffusing Capacity Predicts Cardiac Readmission in Patients Undergoing Left Ventricular Assist Device Implantation in Japan. ASAIO J. 2021 Oct 1; 67(10):1111-1118
10: Bujo C, Amiya E, Hatano M, Tsuji M, Maki H, Ishida J, Ishii S, Narita K, Endo M, Ando M, Shimada S, Kinoshita O, Ono M, Komuro I. Association between infectious event and de novo malignancy after heart transplantation. Heart Vessels. 2021 Apr;36(4):499-508.
11: Yasunaga M, Yasuda Y, Honda A, Maki H, Toyama K, Masamoto Y, Bujo C, Amiya E, Hatano M, Ono M, Komuro I, Kurokawa M. Successful treatment of EBV-related lympho-proliferative disease after heart transplantation with autologous hematopoietic stem cell transplantation despite transient heart failure associated with engraftment syndrome. Ann Hematol. 2021 Apr;100(4):1097-1100.

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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. Yokosu K, Tanabe H, Nomura S, Ozone H, Saito M, Takano H and Okamoto A. Total parietal peritonectomy in primary debulking surgery for advanced ovarian cancer. Gynecologic Oncology Reports. 37:100805, 2021. (available online)
2. Nakamura Y, Okamoto W, Kato T, Esaki T, Kato K, Komatsu Y, Yuki S, Masuishi T, Nishina T, Ebi H, Sawada K, Taniguchi H, Fuse N, Nomura S, Fukui M, Matsuda S, Sakamoto Y, Uchigata H, Kitajima K, Kuramoto N, Asakawa T, Olsen S, Odegaard J I, Sato A, Fujii S, Ohtsu A and Yoshino T. Circulating tumor DNA-guided treatment with pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer: a phase 2 trial. Nat Med. 1-5, 2021.
3. Kobayashi S, Takahashi S, Nomura S, Kojima M, Kudo M, Sugimoto M, Konishi M, Gotohda N, Taniguchi H and Yoshino T. BRAF V600E potentially determines "Oncological Resectability" for "Technically Resectable" colorectal liver metastases. Cancer Medicine: 10(20). 6998-7011, 2021.
4. Sakai T, Udagawa H, Kirita K, Nomura S, Itotani R, Tamiya Y, Sugimoto A, Ota T, Naito T and Izumi H. Comparison of the efficiency of endobronchial ultrasound-guided transbronchial needle aspiration using a 22G needle versus 25G needle for the diagnosis of lymph node metastasis in patients with lung cancer: a prospective randomized, crossover study. Translational Lung Cancer Research: 10(9). 3745, 2021.
5. Nishizawa Y, Nishigori H, Tsukada Y, Sasaki T, Tsukamoto S, Kanemitsu Y, Nakano D, Yamaguchi T, Otsuka K, Nakamura T, Shiomi A, Iwasaki N, Tamura H, Wakabayashi M, Nomura S and Ito M. A multicentre confirmatory single-arm trial of the safety and efficacy of a transanal drain for prevention of anastomotic leakage after surgery for rectal cancer. Colorectal Dis: 2021.
6. Shiraishi Y, Hakozaki T, Nomura S, Kataoka T, Tanaka K, Miura S, Sekino Y, Ando M, Horinouchi H and Ohe Y. A Multicenter, Randomized Phase III Study Comparing Platinum Combination Chemotherapy plus Pembrolizumab with Platinum Combination Chemotherapy plus Nivolumab and Ipilimumab for Treatment-Naive Advanced Non-Small Cell Lung Cancer Without Driver Gene Alterations: JCOG2007 (NIPPON Study). Clinical Lung Cancer: 2021.
7. Uemura Y, Shinozaki T, Nomura S and Shibata T. Comment on "Biostatistical Considerations When Using RWD and RWE in Clinical Studies for Regulatory Purposes: A Landscape Assessment". Statistics in Biopharmaceutical Research. 1-3, 2021.
8. Mamishin K, Naito Y, Nomura S, Ogawa G, Niguma K, Baba K, Sakaeda S, Nakajima H, Kusuhara S and Funasaka C. Comparison of Treatment Completion Rate Between Conventional and Dose-dense Doxorubicin and Cyclophosphamide (AC) Followed by a Taxane in Patients With Breast Cancer: A Propensity Score-matched Analysis. Anticancer Research: 41(12). 6217-6224, 2021.
9. Hasegawa S, Okada A, Aso S, et al. Association Between Diabetes and Major Bleeding Complications of Renal Biopsy. Kidney Int Rep. 2021;7(2): 232-240. Published 2021 Nov 25. doi:10.1016/j.ekir.11.013, 2021
10. Umeoka A, Aso S. Delayed Metastasis of Renal Cell Carcinoma [published online ahead of print, 2021 Dec 4]. Intern Med. 2021; 10.2169/internal medicine.8549-21. doi:10.2169/internalmedicine.8549-21
11. Hattori Y, Tahara S, Aso S, et al. Prophylactic steroid administration and complications after transsphenoidal pituitary surgery: a nationwide inpatient database study in Japan. Br J Anaesth. 2021; 127(2): e41-e43. doi:10.1016/j.bja.2021.04.006
12. Kondo Y, Ohbe H, Aso S, et al. Efficacy of Prophylactic Antibiotics during Extracorporeal Membrane Oxygenation: A Nationwide Cohort Study. Ann Am Thorac Soc. 2021;18(11):1861-1867. doi:10.1513/AnnalsATS.202008-974OC

13. Aso S, Matsui H, Fushimi K, Yasunaga H. Dexmedetomidine and Mortality From Sepsis Requiring Mechanical Ventilation: A Japanese Nationwide Retrospective Cohort Study. J Intensive Care Med. 2021; 36(9): 1036-1043. doi:10.1177/0885066620942154
14. Shigemi D, Isogai S, Uda K, et al. Association between rehabilitation during hospitalization and perinatal outcomes among pregnant women with threatened preterm birth. J Matern Fetal Neonatal Med. 2021; 34(7): 1028-1033. doi:10.1080/14767058.2019.1623197

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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. Tripartite Left Bundle Branch Area Pacing. Hasumi E, Fujiu K. Int Heart J. 2021;62(1):1-3. <2021.1>
2. Percutaneous Mitral Valve Intervention Using

MitraClip for Functional Mitral Regurgitation and Heart Failure. Kaneko H, Kiriyama H, Kamon T, Itoh H, Kodera S, Fujiu K, Daimon M, Morita H, Hatano M, Komuro I. Int Heart J. 2021;62(1):4-8. <2021.1>

3. Impact of hospital volume on clinical outcomes of hospitalized heart failure patients: analysis of a nationwide database including 447,818 patients with heart failure. Kaneko H, Itoh H, Yotsumoto H, Kiriyama H, Kamon T, Fujiu K, Morita K, Michihata N, Jo T, Takeda N, Morita H, Yasunaga H, Komuro I. BMC Cardiovasc Disord. 2021 Jan 25;21(1):49.
4. Association between changes in body weight and lipid profile in the general population: a community-based cohort study. Kiriyama H, Kaneko H, Itoh H, Kamon T, Mizuno Y, Fujiu K, Morita H, Yamamichi N, Komuro I. Eur Heart J Qual Care Clin Outcomes. 2021 Jan 25;7(1): 109-110.
5. Subclinical hypothyroidism as an independent determinant of left atrial dysfunction in the general population. Nakanishi K, Daimon M, Yoshida Y, Sawada N, Hirose K, Iwama K, Yamamoto Y, Ishiwata J, Hirokawa M, Kaneko H, Nakao T, Mizuno Y, Morita H, Di Tullio MR, Homma S, Komuro I. J Clin Endocrinol Metab. 2021 Mar 25;106(4):e1859-e1867.
6. Fasting plasma glucose and subsequent cardiovascular disease among young adults: Analysis of a nationwide epidemiological database. Kaneko H, Itoh H, Kiriyama H, Kamon T, Fujiu K, Morita K, Michihata N, Jo T, Takeda N, Morita H, Yasunaga H, Komuro I. Atherosclerosis. 2021 Feb;319:35-41.
7. Lipid Profile and Subsequent Cardiovascular Disease among Young Adults Aged < 50 Years. Kaneko H, Itoh H, Kiriyama H, Kamon T, Fujiu K, Morita K, Michihata N, Jo T, Takeda N, Morita H, Yasunaga H, Komuro I. Am J Cardiol. 2021 Mar 1;142:59-65.
8. Reverse J-shaped relationship between body mass index and in-hospital mortality of patients hospitalized for heart failure in JapanItoh H, Kaneko H, Kiriyama H, Kamon T, Fujiu K, Morita K, Yotsumoto H, Michihata N, Jo T, Takeda N, Morita H, Yasunaga H, Komuro I. Heart Vessels 2021 Mar;36(3):383-392.
9. Possible association between eating behaviors and cardiovascular disease in the general population: Analysis of a nationwide epidemiological database. Kaneko H, Itoh H, Kiriyama H, Kamon T, Fujiu K, Morita K, Michihata N, Jo T, Takeda N, Morita H, Yasunaga H, Komuro I. Atherosclerosis. 2021 Mar;320:79-85.
10. Cardiac macrophages prevent sudden death during heart stress. Sugita J, Fujiu K, Nakayama Y, Matsubara T, Matsuda J, Oshima T, Liu Y, Maru Y, Hasumi E, Kojima T, Seno H, Asano K, Ishijima A, Tomii N, Yamazaki M, Kudo F, Sakuma I, Nagai R, Manabe I, Komuro I. Nat Commun. 2021 Mar 26;12(1):1910.
11. Application of a Thin-Film Transistor Array for Cellular-Resolution Electrophysiology and Electrochemistry. Anne-Claire Eiler, Pierre-Marie Faure, Sugita J, Ihida S, Dongchen Zhu, Sakai Y, Fujiu K, Komori K, Toshiyoshi H, Agnès Tixier-Mita IEEE Transactions on Electron Devices. 2021 Apr;68(4):2041-2048
12. Surgical treatment for infective endocarditis in the ageing society: a nationwide retrospective study in Japan. Kiriyama H, Kaneko H, Itoh H, Kamon T, Morita K, Jo T, Fujiu K, Daimon M, Takeda N, Morita H, Yasunaga H, Komuro I. Open Heart. 2021 Apr;8(1):e001627.
13. Early Initiation of Feeding and In-Hospital Outcomes in Patients Hospitalized for Acute Heart Failure. Kaneko H, Itoh H, Morita K, Sugimoto T, Konishi M, Kamiya K, Kiriyama H, Kamon T, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Yasunaga H, Komuro I. Am J Cardiol. 2021 Apr 15;145:85-90.
14. Relation of Body Mass Index to Adverse Right Ventricular Mechanics. 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, Komuro I. Am J Cardiol. 2021 Apr 1;144:137-142.
15. Cardiovascular Health Metrics of 87,160 Couples: Analysis of a Nationwide Epidemiological Database Kaneko H, Itoh H, Yotsumoto H, Kiriyama H, Kamon T, Fujiu K, Morita K, Kashiwabara K, Michihata N, Jo T, Morita H, Yasunaga H, and Komuro I. J Atheroscler

Thromb 2021 May 1;28(5):535-543

16. Metabolically Healthy Obesity and the Risk of Cardiovascular Disease in the General Population - Analysis of a Nationwide Epidemiological Database. Itoh H, Kaneko H, Kiriyama H, Kamon T, Fujiu K, Morita K, Michihata N, Jo T, Takeda N, Morita H, Yasunaga H, Komuro I. Circ J. 2021 May 25;85(6):914-920.
17. Association of Blood Pressure Classification Using the 2017 American College of Cardiology/ American Heart Association Blood Pressure Guideline With Risk of Heart Failure and Atrial Fibrillation. Kaneko H, Yano Y, Itoh H, Morita K, Kiriyama H, Kamon T, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Node K, Carey RM, Lima JAC, Oparil S, Yasunaga H, Komuro I. Circulation. 2021 Jun 8;143(23):2244-2253.
18. Sex-specific difference in the association between arterial stiffness and subclinical left ventricular dysfunction. Yoshida Y, Nakanishi K, Daimon M, Ishiwata J, Sawada N, Hirokawa M, Kaneko H, Nakao T, Mizuno Y, Morita H, Di Tullio MR, Homma S, Komuro I. Eur Heart J Cardiovasc Imaging. 2021 Jun 22;22(7):817-823.
19. Detection of significant antiviral drug effects on COVID-19 with reasonable sample sizes in randomized controlled trials: A modeling study. Iwanami S, Ejima K, Kim KS, Noshita K, Fujita Y, Miyazaki T, Kohno S, Miyazaki Y, Morimoto S, Nakaoka S, Koizumi Y, Asai Y, Aihara K, Watashi K, Thompson RN, Shibuya K, Fujiu K, Perelson AS, Iwami S, Wakita T. PLoS Med. 2021 Jul 6;18(7):e1003660.
20. Correlation Between the Cohorts for Heart and Aging Research in Genomic Epidemiology-Atrial Fibrillation Risk Score and Left Atrial Remodeling in the General Population. Hirose K, Nakanishi K, Daimon M, Sawada N, Yoshida Y, Ishiwata J, Hirokawa M, Koyama K, Nakao T, Fujiu K, Morita H, Di Tullio MR, Homma S, Komuro I. Circ Arrhythm Electrophysiol. 2021 Jul;14(7):e009826.
21. Association of Body Mass Index with Ischemic and Hemorrhagic Stroke. Shiozawa M, Kaneko H, Itoh H, Morita K, Okada A, Matsuoka S, Kiriyama H, Kamon T, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Nakamura S, Node K, Yasunaga H, Komuro I. Nutrients. 2021 Jul 9; 13(7):2343.
22. Uninterrupted Direct Oral Anticoagulants Without a Change in Regimen for Catheter Ablation for Atrial Fibrillation Is an Acceptable Protocol. Oshima T, Fujiu K, Matsunaga H, Matsuda J, Matsubara T, Saga A, Yoshida Y, Shimizu Y, Hasumi E, Oguri G, Kojima T, Komuro I. Circ Rep. 2021 Jul 30;3(9):481-487.
23. Possible Gender Difference in the Association Between Abdominal Obesity, Chronic Inflammation, and Preclinical Atherosclerosis in the General Population. Kamon T, Kaneko H, Itoh H, Kiriyama H, Mizuno Y, Morita H, Takeda N, Yamamichi N, Komuro I. Int Heart J. 2021; 62(4):837-842. <2021.7.30>
24. Relation of Serum Uric Acid and Cardiovascular Events in Young Adults Aged 20-49 Years. Seki H, Kaneko H, Morita H, Itoh H, Morita K, Matsuoka S, Kiriyama H, Kamon T, Fujiu K, Michihata N, Jo T, Takeda N, Yano Y, Nakamura S, Node K, Yasunaga H, Komuro I. Am J Cardiol. 2021 Aug 1;152:150-157.
25. Pseudo-elevation of conduction system pacing threshold through parallel connection of an intracardiac electrogram recording system. Yokota J, Fujiu K, Oshima T, Matsubara TJ, Matsuda J, Shimizu Y, Hasumi E, Kojima T, Doi K, Komuro I. J Cardiovasc Electrophysiol. 2021 Aug;32(8):2329-2332.
26. Automatic detection of vessel structure by deep learning using intravascular ultrasound images of the coronary arteries. Shinohara H, Kodera S, Ninomiya K, Nakamoto M, Katsushika S, Saito A, Minatsuki S, Kikuchi H, Kiyosue A, Higashikuni Y, Takeda N, Fujiu K, Ando J, Akazawa H, Morita H, Komuro I. PLoS One. 2021 Aug 5; 16(8):e0255577.
27. Promoting analysis of real-world data: Prospects for preventive cardiology in Japan. Yotsumoto H, Kaneko H, Itoh H, Kamon T, Kiriyama H, Fujiu K, Takeda N, Morita H, Komuro I. Glob Health Med. 2021 Aug 31;3(4):203-213.
28. Risk Factors and Lifestyles in the Development of Atrial Fibrillation Among Individuals Aged 20-39 Years. Itoh H, Kaneko H, Fujiu K, Kiriyama H, Morita K, Kamon T, Michihata N,

Jo T, Takeda N, Morita H, Yasunaga H, Komuro I. Am J Cardiol. 2021 Sep 15;155:40-44.

29. Acute-phase initiation of cardiac rehabilitation and clinical outcomes in hospitalized patients for acute heart failure. Kaneko H, Itoh H, Kamiya K, Morita K, Sugimoto T, Konishi M, Kiriyama H, Kamon T, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Yasunaga H, Komuro I. Int J Cardiol. 2021 Oct 1;340:36-41.
30. Association Between Blood Pressure Classification Using the 2017 ACC/AHA Blood Pressure Guideline and Retinal Atherosclerosis. Matsuoka S, Kaneko H, Yano Y, Itoh H, Fukui A, Morita K, Kiriyama H, Kamon T, Fujiu K, Seki H, Michihata N, Jo T, Takeda N, Morita H, Nakamura S, Yokoo T, Nishiyama A, Node K, Yasunaga H, Komuro I. Am J Hypertens. 2021 Oct 27;34(10):1049-1056.
31. Relation of the Metabolic Syndrome to Incident Colorectal Cancer in Young Adults Aged 20 to 49 Years. Jimba T, Kaneko H, Yano Y, Itoh H, Yotsumoto H, Seki H, Morita K, Kiriyama H, Kamon T, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Nishiyama A, Node K, Yasunaga H, Komuro I. Am J Cardiol. 2021 Nov 1;158:132-138.
32. Corrigendum to: "Fasting plasma glucose and subsequent cardiovascular disease among young adults: Analysis of a nationwide epidemiological database" [Atherosclerosis 319 (2021 Feb) 35-41]. Kaneko H, Itoh H, Kiriyama H, Kamon T, Fujiu K, Morita K, Michihata N, Jo T, Takeda N, Morita H, Yasunaga H, Komuro I. Atherosclerosis. 2021 Nov;336:30-31.
33. Untreated Hypertension and Subsequent Incidence of Colorectal Cancer: Analysis of a Nationwide Epidemiological Database. Kaneko H, Yano Y, Itoh H, Morita K, Kiriyama H, Kamon T, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Nishiyama A, Node K, Bakris G, Miura K, Muntner P, Viera AJ, Oparil S, Lloyd-Jones DM, Yasunaga H, Komuro I. J Am Heart Assoc. 2021 Nov 16;10(22):e022479.
34. Electrical Storm. Kani K, Fujiu K. Int Heart J. 2021;62(6):1195-1198. ＜2021.11＞
35. The Effectiveness of a Deep Learning Model to Detect Left Ventricular Systolic Dysfunction from Electrocardiograms. Katsushika S, Kodera S, Nakamoto M, Ninomiya K, Inoue S, Sawano S, Kakuda N, Takiguchi H, Shinohara H, Matsuoka R, Ieki H, Higashikuni Y, Nakanishi K, Nakao T, Seki T, Takeda N, Fujiu K, Daimon M, Akazawa H, Morita H, Komuro I. Int Heart J. 2021; 62(6):1332-1341. ＜2021.11＞
36. Deep Learning Algorithm to Detect Cardiac Sarcoidosis From Echocardiographic Movies. Katsushika S, Kodera S, Nakamoto M, Ninomiya K, Kakuda N, Shinohara H, Matsuoka R, Ieki H, Uehara M, Higashikuni Y, Nakanishi K, Nakao T, Takeda N, Fujiu K, Daimon M, Ando J, Akazawa H, Morita H, Komuro I. Circ J. 2021 Dec 24; 86(1):87-95.
37. Atrioventricular and Ventricular Functional Interdependence in Individuals Without Overt Cardiac Disease. Yoshida Y, Nakanishi K, Daimon M, Ishiwata J, Sawada N, Hirokawa M, Kaneko H, Nakao T, Mizuno Y, Morita H, Di Tullio MR, Homma S, Komuro I. J Am Heart Assoc. 2021 Dec 7;10(23):e021624.

Laboratory for Advanced Research on Pathophysiology of Metabolic Diseases

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Introduction and Organization

Laboratory for Advanced Research on Pathophysiology of Metabolic Diseases was launched in 2017 to promote cutting-edge research aimed at unraveling the underlying pathophysiology of diabetes and related metabolic diseases thereby contributing to the development of effective preventive measures against these diseases.

"Individuals at risk of diabetes", i.e., those strongly suspected of having diabetes and those in whom the possibility of diabetes cannot be denied, are currently estimated to account for 28.5% of males and 21.4% of females in Japan, thus making it an urgent task not only for metabolic science but for society at large to fully elucidate the underlying pathophysiology of diabetes. Diabetes is defined as a hyperglycemic condition resulting from decreased secretion and/or action of insulin from the pancreas and encompasses a wide disease spectrum from such rare conditions as mitochondrial diabetes and lipoatrophic diabetes to diabetes mellitus as a common disease. Diabetes occurs not only through genetic susceptibility to the disease but due to disorderly living habits, such as overeating, lack of physical activity and obesity. Therefore, the Laboratory is intended to promote wide-ranging research into human tissues from patients with diabetes mellitus as a common disease but from those with rare forms of diabetes by drawing on state-of-the-art genomic, epigenomic, metabolomic, metagenomic and iPS-cell technologies and to bring resulting research insights to bear on the development of innovative diagnostic, preventive and therapeutic modalities for diabetes.

Within the research milieu that the Laboratory offers, therefore, the research currently being promoted is expected to lead to the elucidation of the pathophysiology of diabetes and related metabolic diseases, where rare disease-derived tissue- and iPS cell-based investigations are expected to provide invaluable insights into the pathophysiology of diabetes as a common disease. Thus, the Laboratory is devoted to promoting relevant research leading to the development of innovative diagnostic, preventive and therapeutic modalities, thereby contributing to the effective prevention and treatment of diabetes.

Teaching activities

Working in collaboration with its closely related Laboratory, Departments of Diabetes and Metabolic Disease, Division of Nephrology and Endocrinology, the Laboratory aims to foster internationally-oriented young talents in both an academic and social sense with the focus on graduate students, through the Laboratory's mentoring program for academic dissertations and conference presentations to develop and enhance their science capabilities and skills.

The Laboratory has also had an active role in the clinical researcher development program by the

University of Tokyo, the main aim of which is to impart not only the importance of clinical research but the rudiments of clinical thinking to medical students and clinical researchers in training. As part of Metabolism Research Course on the clinical researcher development program, the Course holds up and pursues, as its research theme, exploration of key molecules involved in the onset/progression of obesity/ type 2 diabetes, given that radical preventive/therapeutic modalities remain yet to be established for the so-called lifestyle-related diseases, which include the metabolic syndrome, type 2 diabetes, obesity, dementia, and frailty, as well as for age-related diseases, all of which are known to occur and progress through interactions between individuals' genetic and environmental factors. Thus, the aim of the program is to explore these key molecules by drawing on the analysis of integrated genomic, epigenomic, transcriptomic, metabolomic and clinical data.

Metabolism Research Course is widely open to medical students and clinicians in training alike to provide support not only for designated themes but for themes of interest to course participants and to foster an infrastructure/environment that would facilitate the presentation of research results at conferences in Japan and overseas as well as their publication as peer-reviewed papers in a timely fashion.

Research activities

Diabetes occurs due not only to genetic factors but to the influence of environmental factors, such as overeating, lack of physical activity, and obesity. Therefore, while diabetes represents a disease condition with a wide spectrum from inherited rare forms of diabetes to diabetes as a common disease, its pathophysiology remains yet to be fully elucidated.

The Laboratory thus focuses on the analysis of the physiological functions of organs and systems that play a key role in the onset of diabetes, i.e., pancreatic endocrine cells, liver, adipose tissue, skeletal muscle, nervous system, immune system and intestinal tract, as well as diseases resulting from disruption of their functions by drawing fully on state-of-the-art omic (genomic, epigenomic, metabolomic, and metagenomic) and iPS-cell technologies and genetic cell and animal engineering.

Research themes also being pursued at the Laboratory include the onset/progression of chronic diseases associated with aging and rare diseases, such as mitochondrial diabetes and lipoatrophic diabetes, to facilitate the development of innovative diagnostic, preventive and therapeutic modalities for these diseases, based on resulting research findings and insights.

References

1. Iwabu M, Okada-Iwabu M, Tanabe H, Ohuchi N, Miyata K, Kobori T, Odawara S, Kadowaki Y, Yokoyama S, Yamauchi T, Kadowaki T. AdipoR agonist increases insulin sensitivity and exercise endurance in AdipoR-humanized mice. Commun Biol. 4, 45, 2021
2. Ohn J, Been KW, Kim JY, Kim EJ, Park T, Yoon HJ, Ji JS, Okada-Iwabu M, Iwabu M, Yamauchi T, Kim YK, Seok C, Kwon O, Kim KH, Lee HH, Chung JH. Discovery of a transdermally deliverable pentapeptide for activating AdipoR1 to promote hair growth. EMBO Mol Med. 13, e13790, 2021
3. Mizuno-Iijima S, Ayabe S, Kato K, Matoba S, Ikeda Y, Dinh TTH, Le HT, Suzuki H, Nakashima K, Hasegawa Y, Hamada Y, Tanimoto Y, Daitoku Y, Iki N, Ishida M, Ibrahim EAE, Nakashiba T, Hamada M, Murata K, Miwa Y, Okada-Iwabu M, Iwabu M, Yagami KI, Ogura A, Obata Y, Takahashi S, Mizuno S, Yoshiki A, Sugiyama F. Efficient production of large deletion and gene fragment knock-in mice mediated by genome editing with Cas9-mouse Cdt1 in mouse zygotes. Methods. 191, 23-31, 2021
4. Hosoe J, Suzuki K, Miya F, Kato T, Tsunoda T, Okada Y, Horikoshi M, Shojima N, Yamauchi T, Kadowaki T. Structural basis of ethnic-specific variants of PAX4 associated with type 2 diabetes. Hum Genome Var. 8, 25, 2021
5. Hosoe J, Kawashima-Sonoyama Y, Miya F, Kadowaki H, Suzuki K, Kato T, Matsuzawa F, Aikawa SI, Okada Y, Tsunoda T, Hanaki K, Kanzaki S, Shojima N, Yamauchi T, Kadowaki T. Genotype-Structure-Phenotype Correlations of Disease-Associated IGF1R Variants and Similarities to Those of INSR Variants. Diabetes. 70, 1874-1884, 2021

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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. Ueda K, Fukuma N, Adachi Y, Numata G, Tokiwa H, Toyoda M, Otani A, Hashimoto M, Liu PY, Takimoto E. Sex Differences and Regulatory Actions of Estrogen in Cardiovascular

System. Front Physiol. 2021 Sep 28;12:738218. doi:10.3389/fphys.2021.738218. PMID: 34650448; PMCID: PMC8505986.

2. Adachi Y, Kiyosue A, Ando J, Kawahara T, Kodera S, Minatsuki S, Kikuchi H, Inaba T, Kiriyama H, Hirose K, Shinohara H, Saito A, Fujiwara T, Hara H, Ueda K, Sakakura K, Hatano M, Harada M, Takimoto E, Akazawa H, Morita H, Momomura SI, Fujita H, Komuro I. Factors associated with left ventricular reverse remodelling after percutaneous coronary intervention in patients with left ventricular systolic dysfunction. Sci Rep. 2021 Jan 8;11(1):239. doi: 10.1038/s41598-020-80491-y. PMID: 33420237; PMCID: PMC7794568.
3. Nakagama Y, Ito M. Towards Deeper Phenotyping of the Dilated Cardiomyopathies in Children - Where Are We Now, and Where Are We Heading? Circ J. 2021 Dec 24;86(1):116-117. doi:10.1253/circj.CJ-21-0802. Epub 2021 Oct 28.
4. Ito M, Morita H. Titin Truncation Variant in Dilated Cardiomyopathy. Int Heart J. 2021;62(2): 221-223. doi: 10.1536/ihj.21-053.
5. Sato T, Ito M. Fibroblast-Cardiomyocyte Interaction in Pediatric Restrictive Cardiomyopathy. Circ J. 2021 Apr 23;85(5):687-689. doi: 10.1253/circj.CJ-21-0100. Epub 2021 Mar 6.
6. Fujiwara T, Takeda N, Hara H, Ishii S, Numata G, Tokiwa H, Maemura S, Suzuki T, Takiguchi H, Kubota Y, Seo K, Sakata A, Nomura S, Hatano M, Ueda K, Harada M, Toko H, Takimoto E, Akazawa H, Nishimura S, Komuro I. Three-Dimensional Visualization of Hypoxia-Induced Pulmonary Vascular Remodeling in Mice. Circulation. 2021 Oct 26;144(17):1452-1455. doi: 10.1161/CIRCULATIONAHA.121.056219. Epub 2021 Oct 25. PMID: 34694894
7. Ishizuka M, Harada M, Nomura S, Ko T, Ikeda Y, Guo J, Bujo S, Yanagisawa-Murakami H, Satoh M, Yamada S, Kumagai H, Motozawa Y, Hara H, Fujiwara T, Sato T, Takeda N, Takeda N, Otsu K, Morita H, Toko H, Komuro I. CXCR7 ameliorates myocardial infarction as a β-arrestin-biased receptor. Sci Rep. 2021 Feb 9;11(1):3426. doi:10.1038/s41598-021-83022-5. PMID:33564089

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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. 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.

In 2021, we accepted a Ph.D. student who aimed to become a medical physicist from the University of Tokushima. He belonged to Professor Akihiro Haga's laboratory, a former Director of the Radiation Management Office, The University of Tokyo Hospital. We provided education about medical physics research and clinical practice to the student. We plan to continue to be involved in the education of physicists and radiation therapists in 2022 and beyond.

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 the study on image quality improvement, we presented a survey on improving the image quality of MVCT using deep learning.

Megavoltage computed tomography (MVCT) is used in helical Tomotherapy for image-guided radiotherapy (IGRT). For precise registration based on image guidance, the quality of MVCT images must be ensured. However, the image quality of MVCT is considerably lower than that of kilovoltage CT (kVCT) and thereby limits the accuracy of IGRT. We developed a deep-learning based model to improve the image quality of MVCT. The image quality of the improved MVCT image was quantitatively evaluated by several image quality indices. As a clinical benefit, it was observed by medical doctors that the improved images enhanced the precision of contouring. Furthermore, we found that our deep-learning based model enables the improvement of the image quality of MVCT while reducing metal artifacts, which often appear in kVCT.

In addition, as a result of the joint research with the Radiation Oncology department, the treatment results of whole-body skin irradiation for Mycosis fungoides using tomotherapy and SBRT in prostate cancer patients with hydrospacer gel indwelling. The results of the phase 2 trial are reported.

Moreover, Dr. Masanari Minamitani, a fourth-year graduate student who was involved in education in this course, has been conducting cancer education in school education, which is the purpose of this course. The program is held at 20 junior high schools in Shinagawa-Ku and Hachioji City, Tokyo, and the number of participants reaches about 2,000.

Research on determining the effectiveness of cancer education was also initiated in collaboration with the Japan Cancer Society. In addition, as a study related to decision-making, we reported the results of a web survey on satisfaction with surgery and radiation therapy among cancer patients. In addition, in the survey report of prostate cancer patients, we also present changes in income before and after treatment.

As cancer education for adults, Nakagawa and Minamitani have asked companies to take action to promote cancer control, a project commissioned by the Ministry of Health, Labour and Welfare chaired by Nakagawa Nakagawa and Minamitani have invited companies to Lectures. In the future, research to verify whether cancer education for adults like this will lead to correct preventive behavior against cancer and an increase in cancer screening rate is also planned.

In February 2022, a joint research project with Daido Life Insurance Co., Ltd. was started on "Cancer Awareness in Small and Medium Enterprises and working status of cancer patients." The content of the research is based on "insurance contract data of small and medium-sized enterprises" held by Daido Life, etc., and Daido Life and the University of Tokyo Hospital jointly analyze trends such as "awareness of cancer" and "employment status of cancer patients" in small and medium-sized enterprises. By utilizing the research results in developing new insurance products and services at Daido Life, etc., we will contribute to "the creation of a workplace environment where people can work with peace of mind even if they have cancer."

As mentioned above, this course conducts various research activities in medical physics and cancer education. Together with human resource development, we expect further evolution from the next fiscal year onwards.

Publications

1: Katano A, Yamashita H, Nakagawa K. Radical radiotherapy for localized cutaneous angiosarcoma of the scalp. Mol Clin Oncol. 2021 Sep; 15(3):195.

2: Minamitani M, Mukai T, Ogita M, Yamashita H, Katano A, Nakagawa K. Relationship between Consulting for Second Medical Opinions, Radiotherapy, and Satisfaction with Therapy, Analyzed by Structural Equation Modeling: A Web-Based Survey. Asian Pac J Cancer Prev. 2021 Sep 1;22(9):2889-2896.

3: Minamitani M, Mukai T, Yamashita H, Katano A, Nakagawa K. Effects on annual income changes after radical radiotherapy versus after prostatectomy in patients with localized prostate cancer with a specific employment status: A web-based pilot study. PLoS One. 2021 Sep 30;16(9): e0258116.

4: Enomoto A, Fukasawa T, Terunuma H, Nakagawa K, Yoshizaki A, Sato S, Miyagawa K. Decrease in MAP3Ks expression enhances the cell death caused by hyperthermia. Int J Hyperthermia. 2022;39(1):200-208.

5: Ozaki S, Kaji S, Nawa K, Imae T, Aoki A, Nakamoto T, Ohta T, Nozawa Y, Yamashita H, Haga A, Nakagawa K. Training of deep cross-modality conversion models with a small data set, and their application in megavoltage CT to kilovoltage CT conversion. Med Phys. 2022 Jun; 49(6):3769-3782.

6: Katano A, Takeuchi K, Yamashita H, Nakagawa K. Stereotactic Body Radiotherapy for a Sacral Metastasis Clarified by Diffusion-Weighted Whole-Body Imaging With Background Body Signal Suppression in a Patient With Castration-Resistant Prostate Cancer. Cureus. 2022 Mar 10; 14(3):e23047.

7: Ogita M, Yamashita H, Nozawa Y, Ozaki S, Sawayanagi S, Ohta T, Nakagawa K. Phase II study of stereotactic body radiotherapy with hydrogel spacer for prostate cancer: acute toxicity and propensity score-matched comparison. Radiat Oncol. 2021 Jun 12;16(1):107.

8: Jinnouchi H, Yamashita H, Kiritoshi T, Miki Y, Katano A, Nakagawa K, Abe O. Prognostic value of pre-treatment maximum standardized uptake value and CRP in radiotherapy of esophageal cancer. Mol Clin Oncol. 2021 Jul;15(1):146.

9: Ogita M, Kawamori J, Yamashita H, Nakagawa K. Palliative radiotherapy for gross hematuria in patients with advanced cancer. Sci Rep. 2021 May 5;11(1):9533..

10: Katano A, Ishida A, Yamashita H, Nakagawa K. Radiotherapy for symptom palliation of splenomegaly in patients with haematological malignancies. Mol Clin Oncol. 2021 Jun;14(6): 114.

11: Kitaguchi M, Yamashita H, Takenaka R, Okuma K, Nawa K, Nakagawa K. Helical Skin Radiation Therapy Including Total Skin Radiation Therapy Using Tomotherapy for Primary Cutaneous Lymphoma With Bone Marrow Suppression as a Related Adverse Event. Pract Radiat Oncol. 2021 May-Jun;11(3):e308-e321.

Department of Molecular Structure and Dynamics

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Teaching activities

We are involved in teaching medical students and Master course and Ph. D. course students in the following lectures and laboratory courses together with the Department of Cell Biology and Anatomy.

I.
1) Lecture on Cell Bilogy, 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 Cenrtral 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, bio-physics, and cellular and molecular neurobiology technique to medical students.

Especially we devote ourselves for the teaching of the cutting edge approaches of new light microscopy such as the Photoactivated Localization Microscopy (PALM), cryo-electron microscopy and X-ray crystallography.

Research activities

Our laboratory studies molecular motors and rail microtubules and the mechanisms of intracellular transport. To study these molecular mechanisms we use new molecular cell biological approaches including cutting edge light microscopies, cryoelectron microscopy of molecular resolution, X-ray crystallography, biophysics, molecular biology and molecular genetics. We aim to study the structure and dynamics of the molecular motors in vitro and in vivo at the highest special and temporal resolution and on these bases try to elucidate functions of molecular motors in vivo combining molecular genetics.

Reference

1. Yoshihara S., Jiang X., Morikawa Mo., Ogawa T., Ichinose S., Yabe H., Kakita A., Toyoshima M., Kunii Ya, Yoshikawa T., Tanaka Y., and **N. Hirokawa.** Betaine ameliorates schizophrenic traits by functionally compensating KIF3-based CRMP2 transport. ***Cell Rep*** 35: 108971, April 13, 1-15,2021 https://doi.prg/10.1016/j. celrep.2021. 108971
2. Morikawa Ma, Jerath N. U., Ogawa T., Morikawa Mo, Tanaka Y., Shy M.E., Zuchner, S., and **N. Hirokawa.** KIF1A mutation of human neurpathies hyperstabilizes the motor-neck interaction in ATPase cycle. ***EMBO J.*** 2022 41:e108899 2021 https://doi.org/10.15252/embj. 2021108899
3. Wang S., Tanaka Y., Xu Y., Takeda S., and **N. Hirokawa.** KIF3B promotes a PI3K signaling gradient causing changes in a Shh protein gradient and suppressing polydactyly in mice. ***Dev Cell*** 57: 2273-2289, 2022 (Cover art) https://doi.org/10.1016/j.devcel.2022.09.007
4. Wan Y., Morikawa Mo., Morikawa M., Iwata S., Naseer I., Caudhary A., Tanaka Y., and **N. Hirokawa.** KIF4 regulates neuronal morphology

and seizure susceptibility via the PARP1 signaling pathway. ***J Cell Biol*** in press 2022

Department of Immunotherapeutics

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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.

References

1. Masuda T, Tanaka N, Takamatsu K, Hakozaki K, Takahashi R, Anno T, Kufukihara R, Shojo K, Mikami S, Shinojima T, Kakimi K, Tsunoda T, Aimono E, Nishihara H, Mizuno R, Oya M. Unique characteristics of tertiary lymphoid structures in kidney clear cell carcinoma: prognostic outcome and comparison with bladder cancer. J Immunother Cancer. 2022 Mar;10(3): e003883.
2. Komura D, Kawabe A, Fukuta K, Sano K, Umezaki T, Koda H, Suzuki R, Tominaga K, Ochi M, Konishi H, Masakado F, Saito N, Sato Y, Onoyama T, Nishida S, Furuya G, Katoh H, Yamashita H, Kakimi K, Seto Y, Ushiku T, Fukayama M, Ishikawa S. Universal encoding of pan-cancer histology by deep texture representations. Cell Rep. 2022 Mar 1;38(9): 110424.
3. Kawanabe-Matsuda H, Takeda K, Nakamura M, Makino S, Karasaki T, Kakimi K, Nishimukai M, Ohno T, Omi J, Kano K, Uwamizu A, Yagita H, Gomperts Boneca I, Eberl G, Aoki J, Smyth MJ, Okumura K. Dietary Lactobacillus-derived exopolysaccharide enhances immune checkpoint blockade therapy. Cancer Discov. 2022 Feb 17: candisc.0929.2021.
4. Sugawara T, Miya F, Ishikawa T, Lysenko A, Nishino J, Kamatani T, Takemoto A,Boroevich KA, Kakimi K, Kinugasa Y, Tanabe M, Tsunoda T. Immune subtypes and neoantigen-related immune evasion in advanced colorectal cancer. iScience. 2022 Jan 6;25(2):103740.
5. Nagaoka K, Sun C, Kobayashi Y, Kanaseki T, Tokita S, Komatsu T, Maejima K,Futami J, Nomura S, Udaka K, Nakagawa H, Torigoe T, Kakimi K. Identification of Neoantigens in Two Murine Gastric Cancer Cell Lines Leading to the Neoantigen-based Immunotherapy. Cancers (Basel). 2021 Dec 27;14(1):106.

6. Saito T, Kurose K, Kojima T, Funakoshi T, Sato E, Nishikawa H, Nakajima J,Seto Y, Kakimi K, Iida S, Doki Y, Oka M, Ueda R, Wada H. Phase Ib study on the humanized anti-CCR4 antibody, KW-0761, in advanced solid tumors. Nagoya J Med Sci. 2021 Nov;83(4):827-840.
7. Maeda Y, Wada H, Sugiyama D, Saito T, Irie T, Itahashi K, Minoura K, Suzuki S, Kojima T, Kakimi K, Nakajima J, Funakoshi T, Iida S, Oka M, Shimamura T, Doi T, Doki Y, Nakayama E, Ueda R, Nishikawa H. Depletion of central memory CD8+T cells might impede the anti-tumor therapeutic effect of Mogamulizumab. Nat Commun. 2021 Dec 14;12(1):7280.
8. Saito N, Kobayashi Y, Nagaoka K, Kushihara Y, Sato Y, Wada I, Kakimi K, Seto Y. Two distinct phenotypes of immunologically hot gastric cancer subtypes. Biochem Biophys Rep. 2021 Nov 3;28:101167.
9. Sun C, Nagaoka K, Kobayashi Y, Nakagawa H, Kakimi K, Nakajima J. Neoantigen Dendritic Cell Vaccination Combined with Anti-CD38 and CpG Elicits Anti-Tumor Immunity against the Immune Checkpoint Therapy-Resistant Murine Lung Cancer Cell Line LLC1. Cancers (Basel). 2021 Nov 2;13(21):5508.
10. Takeuchi Y, Tanegashima T, Sato E, Irie T, Sai A, Itahashi K, Kumagai S, Tada Y, Togashi Y, Koyama S, Akbay EA, Karasaki T, Kataoka K, Funaki S, Shintani Y, Nagatomo I, Kida H, Ishii G, Miyoshi T, Aokage K, Kakimi K, Ogawa S, Okumura M, Eto M, Kumanogoh A, Tsuboi M, Nishikawa H. Highly immunogenic cancer cells require activation of the WNT pathway for immunological escape. Sci Immunol. 2021 Nov 12;6(65):eabc6424.
11. Ma L, Sakamoto Y, Ando K, Fujita H, Takahashi A, Takeshima T, Otsuka H, Ebner DK, Kakimi K, Imai T, Shimokawa T. Th balance related host genetic background affects the therapeutic effects of combining carbon-ion radiotherapy with dendritic cell immunotherapy. Int J Radiat Oncol Biol Phys. 2021 Nov 2:S0360-3016(21)03051-0.
12. Hakozaki K, Tanaka N, Takamatsu K, Takahashi R, Yasumizu Y, Mikami S, Shinojima T, Kakimi K, Kamatani T, Miya F, Tsunoda T, Aimono E, Nishihara H, Mizuno R, Oya M. Landscape of prognostic signatures and immunogenomics of the AXL/GAS6 axis in renal cell carcinoma. Br J Cancer. 2021 Nov;125(11):1533-1543.
13. Takamatsu K, Tanaka N, Hakozaki K, Takahashi R, Teranishi Y, Murakami T, Kufukihara R, Niwa N, Mikami S, Shinojima T, Sasaki T, Sato Y, Kume H, Ogawa S, Kakimi K, Kamatani T, Miya F, Tsunoda T, Aimono E, Nishihara H, Sawada K, Imamura T, Mizuno R, Oya M. Profiling the inhibitory receptors LAG-3, TIM-3, and TIGIT in renal cell carcinoma reveals malignancy. Nat Commun. 2021 Sep 20;12(1):5547.
14. Nishida M, Yamashita N, Ogawa T, Koseki K, Warabi E, Ohue T, Komatsu M, Matsushita H, Kakimi K, Kawakami E, Shiroguchi K, Udono H. Mitochondrial reactive oxygen species trigger metformin-dependent anti-tumor immunity via activation of Nrf2/mTORC1/p62 axis in tumor-infiltrating CD8T lymphocytes. J Immunother Cancer. 2021 Sep;9(9):e002954.
15. Morita M, Nishida N, Sakai K, Aoki T, Chishina H, Takita M, Ida H, Hagiwara S, Minami Y, Ueshima K, Nishio K, Kobayashi Y, Kakimi K, Kudo M: Immunological Microenvironment Predicts the Survival of the Patients with Hepatocellular Carcinoma Treated with Anti-PD-1 Antibody. Liver Cancer 2021.
16. Murakami T, Tanaka N, Takamatsu K, Hakozaki K, Fukumoto K, Masuda T, Mikami S, Shinojima T, Kakimi K, Tsunoda T, Sawada K, Imamura T, Mizuno R, Oya M.Multiplexed single-cell pathology reveals the association of CD8 T-cell heterogeneity with prognostic outcomes in renal cell carcinoma. Cancer Immunol Immunother. 2021 Jul 14.
17. Ahmadi H, Shogen K, Fujita K, Honjo T, Kakimi K, Futami J. Unusual aggregation property of recombinantly expressed cancer-testis antigens in mammalian cells. J Biochem. 2021 Jul 10: mvab081.

Social Cooperation Program

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Introduction and Organization

The Department of Advanced Nursing Technology was established in December 2012 with the aim of developing new academic fields in order to create advanced nursing technology based on clinical evidences. The primary aim is to "Never let patients endure suffering in healthcare;" therefore, our activities aimed to directly assist patients to live longer and have healthier lives.

To date, significant challenges in creating advanced nursing technology have resulted in a gap between academic research and clinical setting requirements. Therefore, strategies of advanced nursing technology have not been applied in hospitals due to its unsuitability in the clinical setting, despite being beneficial to academic nursing researchers at universities.

In contrast, new nursing technologies are often developed by nurses' experiences in clinical settings; however, they have certain limitations such as unavailability of scientific processes. Furthermore, systems to promote and support nurses who wish to conduct research in the clinical setting are insufficient.

The Department of Advanced Nursing Technology was established at the University of Tokyo Hospital (Tokyo, Japan), with the support of Terumo Corp. (Tokyo, Japan), as a social cooperation program. The social cooperation program at the University of Tokyo was established to address the abovementioned challenges and further development of nursing technology. The Department of Advanced Nursing Technology (since in March 2018) now comprises the Department of Gerontological Nursing/Wound Care Management, Department of Nursing, and Department of Hematology and Oncology. This program aimed to develop a new research model through a collaborative research with the Departments of Nursing and Medical Examination of the University of Tokyo Hospital and the Division of Health Sciences and Nursing of the University of Tokyo. In addition, this program aimed to disseminate advances in nursing technology based on the needs of clinical practices worldwide.

The team included the following members from various departments at the University of Tokyo: Ryoko Murayama (Project Associate Professor) and Mari Abe (Project Assistant Professor), as well as Hidenori Tanabe (Visiting Researcher; from Terumo Corp.).

Furthermore, the Global Nursing Research Center (GNRC), Graduate School of Medicine, the University of Tokyo, has been established in April 2017. We were in charge of the department of Clinical Nursing Technology, Division of Care Innovation of GNRC, and contributed to promote research on innovative nursing science and to create an interdisciplinary research and educational environment that fosters young leaders in nursing research.

Teaching activities

This program guided Master's and Ph.D. students from the Department of Gerontological Nursing/ Wound Care management on matters concerning research planning and practical work. Furthermore, we have been involved in providing lectures on topics, such as gerontological nursing and wound care nursing, for undergraduates, master's and Ph.D. students within the Department of Gerontological Nursing/Wound Care management.

We were in charge of lectures on nursing translational research at the seminar hosted by GNRC for post-doctoral fellows and other researchers. (The 9th Introduction seminar to Nursing Science and Engineering)

Research activities

1. Activity policy

A new nursing research scheme aimed at identifying clinical needs related to our primary belief will be developed, i.e., "Never let patients endure suffering in healthcare." Solutions to clinical issues in nursing will be determined using multidisciplinary studies and research. Regarding our scientific approach, epidemiologic surveys and genetic research conducted, followed by evaluation of technologies/devices developed in collaboration with companies, endeavoring to provide epoch-making technologies that meet clinical needs utilizing the Nursing Translational Research system.

Several research projects were conducted in our department, such as development of nursing technology for the early detection of extravasation, clarification of infiltration, identification of mechanisms, development of a new intravenous catheter to prevent catheter failures, and a proposal or new program on infusion therapy management. These projects were being conducted in collaboration with nurses at the University of Tokyo Hospital.

We offered lectures and consultations on research matters and provide guidance on article writing to promote nursing research in the clinical setting. We were planning and running an annual symposium known as "UTokyo nursing research" in order to promote joint research with the Departments of Nursing and Medical Examination and School of Health Science at the University of Tokyo Hospital.

2. Research fields and themes in 2021

- Understanding the mechanisms that lead to peripheral intravenous catheter failures: PIV-CF
- Evaluation of a new intravenous catheter to prevent PIV-CF
- Development of a thermo-film for the early detection of extravasation
- Development of a training program for the technical improvement of peripheral venous catheter placement using ultrasonography

References

1. Takahashi T, Shintani Y, Murayama R, Noguchi H, Abe-Doi M, Koudounas S, et al., Ultrasonographic measurement of blood flow of peripheral vein in the upper limb of healthy participants: a pilot study. Journal of the Japanese Society of Wound, Ostomy, and Continence Management. 2021; 25(3): 576-584.
2. Murayama R, Abe-Doi M, Kogure T, Takahashi T, Kanno C, Ishigaki M, Sanada H. The influence of peripheral intravenous catheterization on the sleep quality of ophthalmic inpatients: An observational study. Journal of Nursing Science and Engineering. 2021; 8: 134-142.
3. Abe-Doi M, Murayama R, Komiyama C, Tateishi R, Sanada H. Effectiveness of ultrasonography for peripheral catheter insertion and catheter failure prevention in visible and palpable veins. Journal of Vascular Access. 2021; doi.org/10.1177/11297298211022078
4. 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; 18(4): e12436.
5. Takahashi T, Murayama R, Abe-Doi M, Miyahara M, Kanno C, Nakagami G, et al., Catheter failure in the administration of hyperosmotic drugs through a peripheral vein and vascular selection: A retrospective cohort study. Drug Discoveries & Therapeutics. 2021; 15(5): 236-240

Department of Medical Information Engineering

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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. Takeda Y, Kin T, Sekine T, Hasegawa H, Suzuki Y, Uchikawa H, Koike T, Kiyofuji S, Shinya Y, Kawashima M, Saito N. Hemodynamic Analysis of Cerebral Arteriovenous Malformations with 3-Dimensional Phase-Contrast Magnetic Resonance Imaging. AJNR 42(12): 2138-2145, 2021
2. Koike T, Kin T, Tanaka S, Sato K Uchida T, Takeda Y, Uchikawa H, Kiyofuji S, Saito T, Takami H, Takayanagi S, Mukasa A, Oyama H, Saito N. Development of new image-guide neuronavigation system: mixed-reality projection mapping is accurate and feasible. Oper Neurosurg 21(6): 549-557, 2021
3. Sugino T, Roth HR, Oda M, Kin T, Saito N, Nakajima Y, Mori K. Performance improvement of weakly supervised fully convolutional networks by skip connections for brain structure

segmentation. Med Phys 48(11): 7215-7227, 2021
4. Sugino T, Kawase T, Onogi S, Kin T, Saito N, Nakajima Y. Loss weightings for improving imbalanced brain structures segmentation using convolutional networks. Healthcase (Basel) 9(8): 938, 2021
5. Ishigami D, Miyawaki S, Nakatomi H, Takayanagi S, Teranishi Y, Ohara K, Hongo H, Dofuku S, Kin T, Abe H, Mitsui J, Komura D, Katoh H, Ishikawa S, Saito N. Brainstem intraparenchymal schwannoma with genetic analysis: a case report and literature review. BMC Med Genomics 14(1): 205, 2021.
6. Yang X, Xia D, Kin T, Igarashi T. A two-step surface-based 3D deep learning pipeline for segmentation of intracranial aneurysm. Electrical Engineering and Systems Science, 2021.
7. Fang H, Yang X, Kin T, Igarashi T. Brain surface reconstruction from MRI images based on segmentation networks applying signed distance maps. IEEE ISBI 2021: 1164-1168
8. Koike T, Kin T, Tanaka S, Takeda Y, Uchikawa H, Shiode T, Saito T, Takami H, Takayanagi S, Mukasa A, Oyama H, Saito N. Development of innovative neurosurgical operation support method using mixed-reality computer graphics. World Neurosurg X. 2021 Mar 13; 11: 100102. doi: 10.1016/j.wnsx.2021.100102. eCollection 2021 Jul.
9. Uchida T, Kin T, Koike T, Kiyofuji S, Uchikawa H, Takeda Y, Miyawaki S, Nakatomi H, Saito N. Identification of the facial colliculus in two-dimensional and three-dimensional images. Neurol Med Chir (Tokyo) 61(6): 376-384, 2021.
10. Uchikawa H, Kin T, Takeda Y, Koike T, Kiyofuji S, Koizumi S, Shiode T, Suzuki Y, Miyawaki S, Nakatomi H, Mukasa A, Saito N. Correlation of inflow velocity ratio detected by phase contrast magnetic resonance angiography with the bleb color of unruptured intracranial aneurysms. World Neurosurg X. 2021 Jan 13; 10: 100098. doi: 10.1016/j.wnsx.2021.100098. eCollection 2021 Apr.
11. Hasegawa H, Kin T, Shin M, Suzuki Y, Kawashima M, Shinya Y, Shiode T, Nakatomi H, Saito N. Possible association between rupture and intranidal microhemodynamics in arteriovenous malformations: phase-contrast magnetic resonance angiography-based flow quantification. World Neurosurg 150: e427-e435, 2021.
12. Kiyofuji S, Kin T, Kakizawa Y, Doke T, Masuda T, Nakatomi H, Morita A, Harada K, Saito N. Development of integrated 3-dimensional computer graphics human head model. Oper Neurosurg 20(6): 565-574, 2021.
13. Sugino T, Suzuki Y, Kin T, Saito N, Onogi S, Kawase T, Mori K, Nakajima Y. Label cleaning and propagation for improved segmentation performance using fully convolutional networks. Int J Comput Assist Radiol Surg 16(3): 349-361, 2021.
14. Nomura S, Kin T, Kunimatsu A, Shojima M, Watanabe Y, Suzuki Y, Shono N, Imai H, Saito T, Nakatomi H, Oyama H, Saito N. Registration method between phase-contrast magnetic resonance angiography and time-of-flight magnetic resonance angiography – A preliminary study. JMIHI 11(1): 33-39, 2021.

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Introduction and Organization

The Department of Healthcare Quality Assessment (HQA) was established in 2006 and has been engaging in research on healthcare quality improvement in collaboration with the Department of Cardiothoracic Surgery in University of Tokyo.

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. In the 21st century, this viewpoint, together with insight from health economics, has been the first priority in the field of medicine and healthcare. "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.

Education and Research

Department of Healthcare Quality Assessment (HQA) has been actively collaborating with healthcare professionals and various academic societies 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 this goal, 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 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 approximately 95% of all surgical operations across Japan in the 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 (as of 2021) more than 5,400 hospitals and clinics are participating in NCD with the accumulated data of 10 million cases (approximately 1.5 million each year).
HQA has developed risk models for different groups of surgical procedures that help us implement 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 a user 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 areas. All of these activities help Japan's healthcare quality initiatives in various places, and HQA is proud of being part of it.

HQA also has conducted evidence-based policy analysis to help federal and local government to develop better healthcare policy-making. It is an academic activity that contributes in a different angle to the endeavor of healthcare quality improvement than those with healthcare professionals in the field, described above. In 2012, HQA started participating in a series of research to evaluate the validity of Japan's cancer control policy framework using various stakeholders' perspectives. Interview as well as questionnaire studies were conducted in accordance with the Basic Plan for Implementing Cancer Control administered by the Japanese Government. Since 2014, HQA has been participating in the conducting post marketing surveillance studies using nationwide registries, 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 subspecialities. HQA supports NCD's systematic data collection, data management, data analyses, and the development of useful feedback systems. Non-surgical fields such as clinical oncology are also joining NCD and this trend is becoming 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 (selected)

1. Hashimoto M, Yamamoto H, Endo S, Okada M, Miyata H, Hasegawa S, et al. Japanese Current Status of Curative-Intent Surgery for Malignant Pleural Mesothelioma. Ann Thorac Surg. 2022 Apr;113(4):1348–53.
2. Ban D, Tanabe M, Kumamaru H, Nitta H, Otsuka Y, Miyata H, et al. Safe Dissemination of Laparoscopic Liver Resection in 27,146 Cases Between 2011 and 2017 From the National Clinical Database of Japan. Ann Surg. 2021 Dec; 274(6):1043–50.
3. Maeda H, Endo H, Ichihara N, Miyata H, Hasegawa H, Kamiya K, et al. Association of day of the week with mortality after elective right hemicolectomy for colon cancer: Case analysis from the National Clinical Database. Ann Gastroenterol Surg. 2021 May;5(3):331–7.
4. Arita J, Yamamoto H, Kokudo T, Hasegawa K, Miyata H, Toh Y, et al. Impact of board certification system and adherence to the clinical practice guidelines for liver cancer on post-hepatectomy risk-adjusted mortality rate in Japan: A questionnaire survey of departments registered with the National Clinical Database. J Hepatobiliary Pancreat Sci. 2021 Oct;28(10): 801–11.
5. Hörer J, Hirata Y, Tachimori H, Ono M, Vida V, Herbst C, et al. Pediatric Cardiac Surgical Patterns of Practice and Outcomes in Japan and Europe. World J Pediatr Congenit Heart Surg. 2021 May;12(3):312–9.
6. Matsuoka T, Ichihara N, Shinozaki H, Kobayashi K, Lefor AK, Kimura T, et al. Antithrombotic drugs have a minimal effect on intraoperative blood loss during emergency surgery for generalized peritonitis: a nationwide retrospective cohort study in Japan. World J Emerg Surg. 2021 May;16(1):27.
7. Fujishiro J, Watanabe E, Hirahara N, Terui K, Tomita H, Ishimaru T, et al. Laparoscopic Versus Open Appendectomy for Acute Appendicitis in Children: a Nationwide Retrospective Study on Postoperative Outcomes. J Gastrointest Surg Off J Soc Surg Aliment Tract. 2021 Apr;25(4): 1036–44.
8. Fujishiro J, Fujiogi M, Hirahara N, Terui K, Okamoto T, Watanabe E, et al. Abdominal Drainage at Appendectomy for Complicated Appendicitis in Children: A Propensity-matched Comparative Study. Ann Surg. 2021 Dec;274(6): e599–604.
9. Ma M, Liu Y, Gotoh M, Takahashi A, Marubashi S, Seto Y, et al. Validation study of the ACS NSQIP surgical risk calculator for two procedures in Japan. Am J Surg. 2021 Nov; 222(5):877–81.
10. Marubashi S, Takahashi A, Kakeji Y, Hasegawa H, Ueno H, Eguchi S, et al. Surgical outcomes in

gastroenterological surgery in Japan: Report of the National Clinical Database 2011-2019. Ann Gastroenterol Surg. 2021 Sep;5(5):639–58.

11. Hosaka A, Kumamaru H, Takahashi A, Azuma N, Obara H, Miyata T, et al. Nationwide study of surgery for primary infected abdominal aortic and common iliac artery aneurysms. Br J Surg. 2021 Apr;108(3):286–95.
12. Hosaka A, Kumamaru H, Usune S, Miyata H, Goto H. Outcomes of Surgery for Endograft Infection in the Abdominal Aorta and Iliac Artery: A Nationwide Cohort Study. Ann Surg. 2021 Nov;

Department of Next-Generation Locomotive Imaging System

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Introduction and Organization

The Department of Next Generation Locomotive Imaging System is established to develop new imaging system for scoliosis deformity in April 2020, which is fully funded by ZOZO Corporation. Screening examinations of scoliosis include the forward bending test and Moiré tomography. However, screening tests such as the forward bending test are not considered accurate enough to detect scoliosis and Moiré tomography is no longer manufactured and cannot be used for school screening examinations. Moreover, radiographic examinations for diagnosing scoliosis requires radiation exposure. Therefore, it is necessary to develop a new screening tool for detecting scoliosis. We aimed to develop a new screening tool for detecting scoliosis using a 3-dimension (3D) measurement bodysuit (ZOZOSUIT®).

Research activities

Our research aim is to develop a new screening imaging system for detecting scoliosis, using a unique 3D body measurement suit (ZOZOSUIT®), which was developed by ZOZO Co.. The development of this new-generation imaging system may detect scoliosis deformity without radiation exposure.

We started the pilot study to establish a protocol for creating a 3D virtual body image using ZOZOSUIT. Specifically, we had the imaging data from subjects with ZOZOSUIT using a smartphone equipped with the application and verified the validity of the acquired body surface data. Shooting position and shooting direction were set and the accuracy of the 3-D body surface data was further evaluated by comparing it with that of a conventional 3-D scanner. The results of validation study showed that a relatively high accuracy of 3-D virtual body image was obtained with a mean error of 3.7 mm. After the improvement of bodysuit (ZOZOSUIT2®), we started to acquire the imaging data in scoliosis patients and healthy controls. We completed the required number of data and proceed the analysis of imaging data. Further investigation on this new screening tool enables us to detect scoliosis deformity more easily and non-invasively.

References

1. 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.*** 2021 Jan 28:2192568221989655. doi: 10.1177/2192568221989655. Online ahead of print. PMID: 33504203
2. Taniguchi Y, Matsubayashi Y, Kato S, Oguchi F, Nohara A, Doi T, Oshima Y, Tanaka S. Tracheal stenosis due to cervicothoracic hyperlordosis in patients with cerebral palsy treated with posterior spinal fusion: a report of the first two cases.

BMC Musculoskelet Disord. 2021 Feb 23;22(1): 217. doi: 10.1186/s12891-021-04094-y.PMID: 33622297

3. Sakai D, Tanaka M, Takahashi J, Taniguchi Y, Schol J, Hiyama A, Misawa H, Kuraishi S, Oba H, Matsubayashi Y, Kato S, Sugawara R, Sato M, Watanabe M, Takeshita K. Cobalt-chromium versus titanium alloy rods for correction of adolescent idiopathic scoliosis based on 1-year follow-up: a multicenter randomized controlled clinical trial. ***J Neurosurg Spine.*** 2021 Mar 19:1-10. doi: 10.3171/2020.9.SPINE 201486. Online ahead of print.PMID: 33740765
4. Nakajima K, Nakamoto H, Kato S, Doi T, Matsubayashi Y, Taniguchi Y, Yoshida Y, Kawamura N, Nakarai H, Higashikawa A, Tozawa K, Takeshita Y, Fukushima M, Iizuka M, Ono T, Shirokoshi T, Azuma S, Tanaka S, Oshima Y. A Multicenter Observational Study on the Postoperative Outcomes of C3 Laminectomy in Cervical Double-door Laminoplasty. ***Clin Spine Surg.*** 2021 May 1;34(4):146-152. doi: 10. 1097/BSD.0000000000001100.PMID: 33086255
5. Nagata K, Nakamoto H, Sumitani M, Kato S, Yoshida Y, Kawamura N, Tozawa K, Takeshita Y, Nakarai H, Higashikawa A, Iizuka M, Ono T, Fukushima M, Sasaki K, Okazaki R, Ito Y, Hara N, Doi T, Taniguchi Y, Matsubayashi Y, Tanaka S, Oshima Y. Diabetes is associated with greater leg pain and worse patient-reported outcomes at 1 year after lumbar spine surgery. ***Sci Rep.*** 2021 Apr 14;11(1):8142. doi: 10.1038/s41598-021-87615-y.PMID: 33854161
6. Kato H, Koga M, Kinoshita Y, Taniguchi Y, Kobayashi H, Fukumoto S, Nangaku M, Makita N, Ito N. Incidence of Complications in 25 Adult Patients With X-linked Hypophosphatemia. Hajime Kato, Minae Koga, Yuka Kinoshita, Yuki Taniguchi, Hiroshi Kobayashi, Seiji Fukumoto, Masaomi Nangaku, Noriko Makita, Nobuaki Ito. ***J Clin Endocrinol Metab.*** 2021 Aug 18;106(9): e3682-e3692. doi: 10.1210/clinem/dgab282. PMID: 33912912
7. Otomo N, Lu HF, Koido M, Kou I, Takeda K, Momozawa Y, Kubo M, Kamatani Y, Ogura Y, Takahashi Y, Nakajima M, Minami S, Uno K, Kawakami N, Ito M, Sato T, Watanabe K, Kaito T, Yanagida H, Taneichi H, Harimaya K, Taniguchi Y, Shigematsu H, Iida T, Demura S, Sugawara R, Fujita N, Yagi M, Okada E, Hosogane N, Kono K, Nakamura M, Chiba K, Kotani T, Sakuma T, Akazawa T, Suzuki T, Nishida K, Kakutani K, Tsuji T, Sudo H, Iwata A, Kaneko K, Inami S, Kochi Y, Chang WC, Matsumoto M, Watanabe K, Ikegawa S, Terao C. Polygenic Risk Score of Adolescent Idiopathic Scoliosis for Potential Clinical Use. ***J Bone Miner Res.*** 2021 Aug; 36(8):1481-1491. doi: 10.1002/jbmr.4324. Epub 2021 Jun 22.PMID: 34159637
8. Takeda N, Inuzuka R, Yagi H, Morita H, Ando M, Yamauchi H, Taniguchi Y, Porto KJ, Kanaya T, Ishiura H, Mitsui J, Tsuji S, Toda T, Ono M, Komuro I. Clinical Impact of Copy Number Variation on the Genetic Diagnosis of Syndromic Aortopathies. ***Circ Genom Precis Med.*** 2021 Aug;14(4):e003458. doi: 10.1161/CIRCGEN.121. 003458. Epub 2021 Jul 30.PMID: 34325513
9. Nakajima K, Nakamoto H, Nakarai H, Nagata K, Kato S, Doi T, Matsubayashi Y, Taniguchi Y, Kawamura N, Higashikawa A, Takeshita Y, Fukushima M, Ono T, Hara N, Azuma S, Tanaka S, Oshima Y. Risk factors for worsening sexual function after lumbar spine surgery and characteristics of non-responders to the questionnaire of sex life. ***Eur Spine J.*** 2021 Sep; 30(9): 2661-2669. doi: 10.1007/s00586-021-06867-4. Epub 2021 May 18.PMID: 34003382
10. Okamoto N, Kato S, Doi T, Matsubayashi Y, Taniguchi Y, Yoshida Y, Kawamura N, Nakarai H, Higashikawa A, Tozawa K, Takeshita Y, Yu J, Hara N, Sasaki K, Azuma S, Tanaka S, Oshima Y. Relative Risks and Benefits of Crossing the Cervicothoracic Junction During Multilevel Posterior Cervical Fusion: A Multicenter Cohort. ***World Neurosurg.*** 2021 Sep;153:e265-e274. doi: 10.1016/j.wneu.2021.06.091. Epub 2021 Jun 25. PMID: 34175484
11. Taniguchi Y, Matsubayashi Y, Kato S, Doi T, Takeda N, Yagi H, Inuzuka R, Oshima Y, Tanaka S. Predictive Physical Manifestations for Progression of Scoliosis in Marfan Syndrome. ***Spine (Phila Pa 1976).*** 2021 Aug 1;46(15):1020-1025. doi: 10.1097/BRS.0000000000003939. PMID: 34228694

12. Okamoto N, Kato S, Doi T, Nakamoto H, Matsubayashi Y, Taniguchi Y, Inanami H, Higashikawa A, Kawamura N, Hara N, Azuma S, Takeshita Y, Ono T, Fukushima M, Tanaka S, Oshima Y. Influence of Perioperative Antithrombic Agent Discontinuation in Elective Posterior Spinal Surgery: A Propensity-Score-Matched Analysis. ***World Neurosurg***. 2022 Feb; 158:e362-e368. doi: 10.1016/j.wneu.2021.10.182. Epub 2021 Nov 4.PMID: 34743017
13. Saiki F, Tanaka T, Tachibana N, Oshima H, Kaneko T, Horii C, Nakamoto H, Kato S, Doi T, Matsubayashi Y, Taniguchi Y, Tanaka S, Oshima Y. Effect of Spinal Alignment Changes on Lower Back Pain in Patients Treated with Total Hip Arthroplasty for Hip Osteoarthritis. ***Medicina (Kaunas)***. 2021 Nov 9;57(11):1219. doi: 10. 3390/medicina57111219.PMID: 34833437
14. 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.*** 2021 Dec 16:jmedgenet-2021-108186. doi: 10.1136/jmedgenet-2021-108186. Online ahead of print.PMID: 34916231
15. Ohtomo N, Nakamoto H, Miyahara J, Yoshida Y, Nakarai H, Tozawa K, Fukushima M, Kato S, Doi T, Taniguchi Y, Matsubayashi Y, Higashikawa A, Takeshita Y, Kawamura N, Inanami H, Tanaka S, Oshima Y. Comparison between microendoscopic laminectomy and open posterior decompression surgery for single-level lumbar spinal stenosis: a multicenter retrospective cohort study. ***BMC Musculoskelet Disord.*** 2021 Dec 20;22(1):1053. doi:10.1186/s12891-021-04963-6.PMID:34930238
16. Demura S, Hinoi E, Kawakami N, Handa M, Yokogawa N, Hiraiwa M, Kato S, Shinmura K, Shimizu T, Oku N, Annen R, Kobayashi M, Yamada Y, Nagatani S, Iezaki T, Taniguchi Y, Tsuchiya H. The L-type Amino Acid Transporter (LAT1) Expression in Patients with Scoliosis. ***Spine Surg Relat Res.*** 2021 Dec 27;6(4):402-407. doi: 10.22603/ssrr.2021-0189. eCollection 2022. PMID: 36051676

Next-Generation Precision Medicine Development Laboratory

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Project Lecturer
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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 Head of Cell Informatics, at National Cancer Center 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. Kage is involved in cancer genomic medicine at The University of Tokyo Hospital through oversight of the Expert Panel.

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 2021, 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 and (2) association of tumor mutational burden and immune checkpoint efficacy using TOP.

(1) Best tissue processing practices for CGP tests with RNA panel
Background: Formalin-fixed, paraffin-embedded (FFPE) samples are valuable resources routinely used in pathology, and generally used for clinical CGP tests. However, the preparation of these samples requires multiple stages, that are far from standardised, especially for RNA sequencing. Since preanalytical

sample processing ultimately impacts sequencing accuracy and reproducibility, its optimization is essential. RNA from FFPE tissues may be more prone to being chemically modified, cross-linked and degraded over time due to fixation and archiving methods than DNA. Therefore, RNA sequencing may be more difficult than DNA analysis, which has been more standardized. We examined the best practice for tissue processing for extracting high-quality DNA/RNA for CGP tests with RNA panels.
Methods: <1> Nucleic Acid Requirements; Fourteen FFPE blocks from 6 tissue types were sectioned, and the DNA and RNA were extracted either separately or simultaneously. <2> Storage Duration and Temperature; To validate the impact of storage duration and temperature of the FFPE sections, specimens were preserved in a tube at room temperature, 4, -20, or -80 degrees Celsius for 1 week or 1 month. Subsequently, the quality of DNA/RNA was evaluated.
Results: The type of extraction methods and storage duration or temperature did not affect the DNA/RNA purification efficiency. The average DNA/RNA yield from all tissue types tested was comparable regardless of the method.
Conclusions: The DNA/RNA yield and the quality of various tissue types were comparable between DNA/RNA extracted simultaneously from one sample and DNA/RNA extracted in individual procedures. The simultaneous purification method can maximize the use of precious sample materials. Storage of the sections at room temperature for one week or one month in a tube both met the sample requirement for CGP tests.

(2) Tumor mutational burden (TMB) measurement using TOP
Background: Tumors with a high number of mutations in the genome, or tumor mutational burden (TMB), are presumed to be more likely to respond to immune checkpoint inhibitors. However, the optimal method to calculate TMB using comprehensive genomic profiling assays is unknown. TOP DNA panel version 6 is an improvement over version 3 with increased number of targeted genes and limited targeting of intronic regions.
Methods: We calculated TMB using TOP and compared them with whole exosome sequencing (WES) TMB. In addition, 16 lung cancer patients had their samples analyzed with TOP and were treated with anti-PD-1 or PD-L1 antibody monotherapy.
Results: When compared with WES, TMB measured by TOP resulted in correlation efficiency of 0.96-0.97. When WES TMB of 10 or higher was considered TMB-high, TOP TMB high showed sensitivity of 0.88-1.0 and specificity of 0.93. Patients with either partial response or stable disease showed a trend towards higher TMB and higher PD-L1 expression compared with patients with progressive disease.
Conclusions: Increase in targeted gene number and limiting intronic regions improved TMB measurement by TOP when compared with WES TMB.

Publications

1. Ikushima H, Hiraishi Y, Toriumi K, Ando T, Tamiya H, Ishida J, Amano Y, Kage H, Tanaka G, Nagase T. Multiple cerebral infarctions in ROS1-rearranged lung adenocarcinoma. Respirol Case Rep 2021;9:e0831. PMID: 34471540
2. Kurokawa R, Inui S, Gonoi W, Nakai Y, Ishida M, Watanabe Y, Kubo T, Amano Y, Okamoto K, Kage H, Harada S, Tanaka G, Kawahara T, Nagase T, Moriya K, Abe O. Standardized reporting systems of chest computed tomography in a population with low coronavirus disease 2019 prevalence: A retrospective comparative study. Heliyon 2021;7: e07743. PMID: 34395930
3. Ando T, Kage H, Matsumoto Y, Zokumasu K, Nagase T. Lower dose of ethambutol may reduce ocular toxicity without radiological deterioration for Mycobacterium avium complex pulmonary disease. Respir Investig 2021;59:777-782. PMID: 34389250
4. Manaka K, Sato J, Takeuchi M, Watanabe K, Kage H, Kawai T, Sato Y, Miyagawa T, Yamada D, Kume H, Sato S, Nagase T, Iiri T, Nangaku M, Makita N. Immune checkpoint inhibitor combination therapies very frequently induce secondary adrenal insufficiency. Sci Rep 2021;11:11617. PMID: 34078988
5. Amano Y, Kage H, Tanaka G, Gonoi W, Nakai Y, Kurokawa R, Inui S, Okamoto K, Harada S, Iwabu M, Morizaki Y, Abe O, Moriya K, Nagase T. Diagnostic prediction of COVID-19 based on clinical and radiological findings in a relatively

low COVID-19 prevalence area. Respir Investig 2021;59:446-453. PMID: 33865743

6. Imai S, Ooki T, Murata-Kamiya N, Komura D, Tahmina K, Wu W, Takahashi-Kanemitsu A, Knight CT, Kunita A, Suzuki N, Del Valle AA, Tsuboi M, Hata M, Hayakawa Y, Ohnishi N, Ueda. Helicobacter pylori CagA elicits BRCAness to induce genome instability that may underlie bacterial gastric carcinogenesis. Cell Host Microbe 2021;6:941-958. PMID: 33989515
7. Abe H, Kunita A, Otake Y, Kanda T, Kaneda A, Ushiku T, Fukayama M. Virus-host interactions in carcinogenesis of Epstein-Barr virus-associated gastric carcinoma: Potential roles of lost ARID1A expression in its early stage. PLoS One 2021;9: e0256440. PMID: 34469459
8. Iwasaki A, Shinozaki-Ushiku A, Kunita A, Yamazawa S, Sato Y, Yamashita H, Fukayama M, Seto Y, Ushiku T. Human Leukocyte Antigen Class I Deficiency in Gastric Carcinoma: An Adaptive Immune Evasion Strategy Most Common in Microsatellite Instable Tumors. Am J Surg Pathol 2021;45:1213-1220. PMID: 34310369

Department of Tissue Stem Cells and Life Dentistry

Project Professor

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Project Lecturer

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Introduction and Organization

A social cooperation course, The Department of Tissue Stem Cells and Life Dentistry was established on November 1st, 2019, with the cooperation of SheepMedical Co., Ltd. (formerly Dental Assist Co., Ltd.), Fukekai medical corporation Fuke Hospital, Sankeikai medical corporation Sashiogi Hospital, Kayuukai medical corporation Ikegami Home Clinic, and Inotech Co., Ltd.

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. Specifically, using cells that constitute the fibrillary connective tissue (BIOSHEET / BIOTUBE) that encapsulates around cells and tissues such as dental pulp stem cells, adipose tissue-derived stem cells or even a mold that is transplanted subcutaneously. Furthermore, a research on the correlation between oral environment and systemic diseases / intestinal environment is in preparation process.

The department is currently headed by a Project Professor, was formerly 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 December 21, 2021, 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
- 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

References

1: Suzuki K, Komura M, Obana K, Komura H, Inaki R, Fujishiro J, Suzuki K, Nakayama Y. A new method of primary engineering of esophagus using orthotopic in-body tissue architecture. J Pediatr Surg. 2021 Jul;56(7):1186-1191.

2: Kanazawa S, Okada H, Hojo H, Ohba S, Iwata J, Komura M, Hikita A, Hoshi K. Mesenchymal stromal cells in the bone marrow niche consist of multi-populations with distinct transcriptional and epigenetic properties. Sci Rep. 2021 Aug 4;11(1): 15811.

3: Miyamoto Y, Kubota K, Asawa Y, Hoshi K, Hikita A. M1-like macrophage contributes to chondrogenesis in vitro. Sci Rep. 2021 Oct 29;11(1): 21307.

4: Kanda K, Asawa Y, Inaki R, Fujihara Y, Hoshi K, Hikita A. Requirement of direct contact between chondrocytes and macrophages for the maturation of regenerative cartilage. Sci Rep. 2021 Nov 18; 11(1):22476.

Department of Prevention of Diabetes and Lifestyle-Related Diseases

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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 clinical characteristics of insulinoma
Little information on recent clinical practice in patients with insulinoma is available. Using a nationwide inpatient database, we identified clinical characteristics of benign and malignant insulinoma in Japan.

4) Research on potassium replacement therapy for diabetic ketoacidosis
Guidelines worldwide recommend potassium replacement of 10 to 40 mmol/L in the initial fluid therapy for patients with diabetic ketoacidosis. However, evidence is lacking as to the association between infused potassium concentration and mortality. Using a nationwide inpatient database, we showed that patients receiving potassium replacement at concentrations of 10 to 40 mmol/L had similar in-hospital mortality rates, whereas lower concentrations were associated with higher mortality.

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. Momose A, Yamaguchi S, Okada A, Ikeda-Kurakawa K, Namiki D, Nannya Y, et al. Factors associated with long-term care certification in older adults: a cross-sectional study based on a nationally representative survey in Japan. BMC Geriatr. 2021;21(1):374.
2. Kurakawa KI, Okada A, Manaka K, Konishi T, Jo T, Ono S, et al. Clinical characteristics and incidences of benign and malignant insulinoma using a national inpatient database in Japan. J Clin Endocrinol Metab. 2021.
3. Okada A, Yamana H, Morita K, Sato Y, Yamaguchi S, Kurakawa KI, et al. Potassium concentration in initial fluid therapy and in-hospital mortality of patients with diabetic ketoacidosis. J Clin Endocrinol Metab. 2021.
4. Okada A, Ono S, Yamaguchi S, Yamana H, Ikeda Kurakawa K, Michihata N, et al. Association between nutritional guidance or ophthalmological examination and discontinuation of physician visits in patients with newly diagnosed diabetes: A retrospective cohort study using a nationwide database. J Diabetes Investig. 2021;12(9):1619-31.
5. Okada A, Yamana H, Yamaguchi S, Kurakawa KI, Michihata N, Matsui H, et al. 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. 2021.
6. Sato Y, Morita K, Okada A, Matsui H, Fushimi K, Yasunaga H. Factors affecting in-hospital mortality of diabetic ketoacidosis patients: A retrospective cohort study. Diabetes Res Clin Pract. 2021;171:108588.

Department of Pain and Palliative Medical Sciences

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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 Mediccal 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. Mietani K, et al. Elevateed neuron-specific enolase level is associated with postoperative delirium and detection of phosphorylated neurofilament heavy subunit: A prospective observational study. *PLoS ONE 2021; 16: e0259217*
2. The OSCIS investigators. Effect of early vs delayed surgery on motor recovery in incomplete cervical spinal cord injury with pre-existing cervical stenosis: a randomized clinical trial. *JAMA Network Open 2021; 4: e2133604*
3. Inoue R, et al. Capecitabine-induced hand-foot syndrome does not emerge in the complex regional pain syndrome-affected limb: Case Report. *Mol Clin Oncol 2021; 15: 254*
4. Kato K, et al. Development of a severity discrimination scale based on physical quality of life for patients with chronic pain. *J Orthop Sci 2021; 26: 1124-9*
5. Osumi M, et al. Fear of movement-related pain disturbs cortical preparatory activity after

becoming aware of motor intention. *Behav Brain Res 2021; 411: 113379*

6. Osumi M, et al. Pain quality of thermal grill illusion is similar to that of central neuropathic pain rather than peripheral neuropathic pain. *Scand J Pain 2021; 22: 40-7*
7. Tsuchida R, et al. Genetic polymorphisms of lysophosphatidic acid receptor 1 are associated with the onset of taxane-induced peripheral neuropathy. *Br J Anaesth 2021; 127: e43-6*
8. Sumitani M. Time to act for reappraising the educational system for universal access to opioid analgesics, for quality palliative care and cancer-related pain relief in East Asian countries. *Lancet Regional Health – Western Pacific 2021; 16: 100270*
9. Saita K, et al. Exponential correlations among neuropathic components, pain intensity and catastrophic thoughts in patients with musculoskeletal pain disorder. *Curr Med Res Opin 2021; 37: 1341-8*
10. Ikeda K, et al. Required research activities to overcome addiction problems in Japan. *Taiwan J Psychiatr 2021; 35: 6-11*
11. Uranbileg B, et al. Inhibition of autotaxin activity ameliorates neuropathic pain derived from lumbar spinal stenosis. *Scientific Reports 2021; 11: 3984*
12. Ando M, et al. Tele virtual reality-based peer support programme for cancer patients: a preliminary feasibility and acceptability study. *Br J Cancer Res 2021; 3: 443-8*
13. Nagata K, et al. Diabetes is associated with greater leg pain and worse patient-reported outcomes at one year after lumbar spine surgery. *Scientific Reports 2021; 11: 8142*
14. Owada H, et al. Peripheral nerve field stimulation successfully manages axial pain after posterior cervical spine surgery: case report. *Ann Palliat Med 2021; 10: 579-96*
15. Nishi Y, et al. Kinematic change in goal-directed movements in a fear-conditioning paradigm. *Scientific Reports 2021; 11: 11162*
16. Kaizu M, Komatsu H, Yamauchi H, et al. Characteristics of taste alterations in people receiving taxane-based chemotherapy and their association with appetite, weight and quality of life. *Supp Care Cancer 2021; 29: 5103-14*

(And, 18 Japanese articles)

Department of Innovative Dementia Prevention

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Introduction and Organization

Department of Innovative Dementia Prevention was launched on July 2017, through the financial support of Kobayashi Pharmaceuticals, with assistance by the Department of Neuropathology. Two faculty staffs, Tadafumi Hashimoto as the Project Associate Professor and Ryoko Ihara as the Project Assistant Professor started the research projects, with Dr. Daisuke Izawa of Kobayashi as a collaborative researcher. From January 2019, Dr. Tomoko Wakabayashi joined in the department in the replacement of Dr. Ryoko Ihara, and Dr. Yutaro Ito of Kobayashi also joined in the research project in the replacement of Dr. Izawa. Dr. Hashimoto has moved out in September 2021, and Dr. Wakabayashi has taken up the Project Associate Professor in December 2021.

The aged society in Japan urges us to challenge the dementing disorders including Alzheimer's disease (AD), although there have emerged no effective therapeutic strategies against AD based on its pathomechanism. Our laboratory will conduct basic research on the molecular mechanism of dementia and development of clinical measures for evaluation of efficacies of the therapeutic drugs in parallel, aiming at identifying the novel targets for prevention and early treatment of dementia and establish methods to prevent or delay the progression of dementia by drugs and functional foods. We also will be actively involved in the education and outreach activities of basic and clinical research on AD and dementia.

Education

Department of Innovative Dementia Prevention was involved in the education through research activities of graduate students of the Graduate School of Medicine and medical student belonging to the Medical Scientist Training Program. In addition, TH has given a lecture on "Special Lecture Basic Pharmaceutical Science IV" to students belonging to the Graduate School of Pharmaceutical Sciences.

Research

Department of Innovative Dementia Prevention is conducting research in the following four directions, based on the amyloid hypothesis of AD, toward the goal of developing strategies for prevention of dementia and AD.

① Molecular mechanism of Aβ dynamics in the brain

Amyloid β peptide (Aβ), a causative protein for AD, is produced from the amyloid precursor protein (APP) through two-step proteolysis by β- and γ-secretases, and then secreted into the extracellular space. Once released outside the neurons, Aβ is readily cleared by proteolytic degradation or transported outside the brains. However, Aβ that escaped from the clearance starts to aggregate and deposit forming amyloid fibrils. Thus, the elucidation of the Aβ dynamics in the brain, comprised of the elementary processes of "production", "secretion", "aggregation" and "deposition", is vital to the clarification of the pathogenic mechanism of AD as well as development of therapeutic and prevention

strategies against AD. However, to quantitatively analyze each of the process, there is a compelling need for accurate quantitation of Aβ that is present at picomolar levels in brains.

We have adopted the microdialysis technique using dialysis membrane of ~1,000 kDa cut-off that enables the recovery of brain interstitial fluids and quantitation of the levels, rates of production and clearance of Aβ in the hippocampus and other parts of the brains (Yamamoto K, et al., Cell Rep., 2015). In combination with the in vivo seeding experiments injecting aggregation seeds for Aβ and evaluate the following Aβ deposition (Hori Y, et al., J. Biol. Chem., 2015), we have identified a >200 kDa high molecular weight (HMW) Aβ oligomer species in the soluble fractions of brains of APP transgenic mice and AD brains (Hashimoto T, Soc for Neuroscience meeting 2017), and found that oligomeric structure of HMW Aβ is essential for the induction of β-amyloidosis. We also found that the level of HMW Aβ oligomers in the brains of amyloid angiopathy-rich AD cases were significantly higher than those of amyloid angiopathy-minimal AD cases, suggesting that seed-competent HMW Ab oligomers may accumulate in the amyloid angiopathy in the brains of AD patients. We will further identify Aβ species that are involved in the Aβ dynamics in the brain, including those specifically involved in deposition or toxicity of Aβ.

② Elucidation of the role of apolipoprotein E (apoE) in the pathogenesis of AD, and development of method of AD prevention targeting apoE

Apolipoprotein E (apoE) is produced by astrocytes and comprises the major lipoprotein in the central nervous system. Human APOE gene has three genetic polymorphisms (ε2, ε3, ε4), resulting in the production of three protein isoforms (apoE2, apoE3, apoE4) harboring different amino acids at two critical residues at positions 112 and 158. The allele frequency of ApoE ε4 allele is ~8-10% in normal population, whereas it is elevated to >30-40% in AD. Thus, ApoE ε4 is a strong genetic risk factor of AD, although the mechanism whereby ApoE ε4 accelerates AD pathophysiology has remained elusive, without any effective therapeutic strategies targeting apoE.

We have created a series of bigenic mice by crossing knock-in (KI) mice expressing human apoE2, E3 or E4 with APP transgenic mice, and we are currently trying to examine how each human isoform of apoE influences on Aβ dynamics in the brain. This will lead us to the intervention into the effect of apoE isoforms on Aβ, toward the goal of AD prevention. We have found a significant decrease in Aβ deposition in the brains of human apoE3 KI/APP transgenic mice. Using in vivo seeding technique, we have also found that apoE3 suppressed the deposition of Aβ compared with murine apoE, and that apoE4 was less able to suupress the Ab deposition compared to apoE3. We further found that deletion of the APOE gene in APP tg mice markedly reduced Aβ deposition, and that no Ab deposition was induced by in vivo seeding experiment in the brain of APPtg/apoE KO mice. These data suggested that apoE is an essential factor for Aβ deposition (Hashimoto T, Soc for Neuroscience meeting 2021). In vivo microdialysis experiments, we found that the Aβ levels in the interstitial fluids of human apoE3 KI/APP transgenic mice are similar to those in APP transgenic mice by method. We also have established a method to monitor the interaction between Aβ and apoE using a bi-molecular complementation assay. We will use this unique assay system to identify small molecule drugs that modulate the interaction of apoE and Aβ.

③ Establishment of a novel AD model using three-dimensional culture system for the development of prevention methods targeting brain Aβ metabolism.

To overcome the lack of experimental paradigms for the evaluation of aggregation and deposition in vitro, we adopted 3-dimensional culture system using Matrigel for the neuronal differentiation of human ReNcell-VM neuronal precursor cells, to observe the process of Aβ deposition and Aβ-dependent neurotoxicity reminiscent to that in AD brains. In 2018, we found the phosphorylation of tau by the overproduction of E22G mutant Aβ in the ReNcell-VM neurons. We will use this system for the development of anti-dementia drugs targeting Aβ production and deposition.

④ Clinical studies on the clinical and cognitive measures in the early stages of AD.

We have set out to the systematic analysis of the clinical data on the natural course of the early stage of

AD derived from Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI), with a special focus on the preclinical AD stage, where elderly individuals are clinically and cognitively normal but positive for amyloid biomarkers. We have found that preclinical AD individuals lack learning effects in the cognitive tests, e.g., MMSE and logical memory, presumably representing subtle cognitive deficits. We also aim at international harmonization and comparison of the evaluation of cognitive decline, using US-ADNI database and other international datasets.

⑤ Molecular mechanisms linking type II diabetes mellitus and Alzheimer's disease

A number of epidemiological studies have reported that type 2 diabetes increases the risk of developing Alzheimer's disease (AD) by about twofold. Studies using human autopsy brains, imaging analysis, and mouse models suggest that insulin resistance, a central pathology of diabetes, may be correlated with amyloid accumulation. In addition, analysis of Alzheimer's patient brains has shown that insulin signaling may be impaired in AD brains, suggesting that insulin resistance may be a common pathology in both diseases. Based on these findings, activation of insulin signaling in the brain is being explored as a new target for AD therapy. Therefore, we are investigating the effects of metabolic abnormalities such as diabetes or of genetic suppression of insulin signaling on the formation of amyloid pathology and its molecular mechanisms.

In order to elucidate the molecular mechanisms linking type 2 diabetes and AD, especially the effects on amyloid pathogenesis, we have been conducting analyses using APP Tg mice (A7 strain), a mouse model of Alzheimer's disease. In APP Tg mice, which were fed a high-fat diet (HFD) from 3 months of age and developed a diabetic-like condition, there was a decrease in brain responsiveness to insulin stimulation in addition to systemic insulin resistance. In this mouse, the amount of Aβ in the brain increased significantly with age compared to the normal diet group, and the accumulation of amyloid plaques was also accelerated at 15 months of age. In vivo kinetic analysis showed that this might be partly due to a decrease in Aβ clearance in the brain caused by HFD feeding.

We then analyzed the contribution of IRS-1 and IRS-2, substrates of insulin and IGF-1 receptors, to brain signaling activity and found that IRS-2 is mainly involved in brain insulin signaling. While loss of IRS-1 did not affect the pathology of the APP Tg mouse brain, IRS-2 deficiency markedly suppressed amyloid accumulation in the brain, even though it triggered systemic insulin resistance and led to diabetes (Ochiai et al., Neurobiol Dis 2021). By contrast, amyloid accumulation was accelerated when IRS-2-deficient APP Tg mice were fed with HFD. This suggests that upstream factors, such as stress associated with metabolic overload, rather than decreased insulin signaling, may be responsible for accelerated amyloid accumulation (Wakabayashi et al., Mol Neurodegener 2019).

One of the factors contributing to insulin resistance is endoplasmic reticulum (ER) stress, which is altered by metabolic stress. In HFD-fed and genetically obese animals, ER stress in liver and adipose tissue is increased and unfolded protein response (UPR) signaling is elevated. Inhibiting ER stress has been shown to improve insulin resistance. It has also been reported that ER stress is elevated in the brains of Alzheimer's disease patients, suggesting that it may be an aggravating factor in both diseases. Therefore, the chemical chaperone TUDCA was administered to the periphery or brain of aging or HFD-fed APP Tg mice with metabolic abnormalities to analyze the effects of reduced endoplasmic reticulum stress on Aβ accumulation. The results showed that administration of TUDCA to the periphery, but not to the brain, markedly suppressed amyloid accumulation in the brain. This suggests that stress and inflammation induced in peripheral tissues due to metabolic abnormalities may directly regulate brain pathology (Ochiai et al., J Prev Alzheimer Dis 2021).

The mechanism by which IRS-2 deficiency has a protective effect on Aβ accumulation has not yet been elucidated. Deficiency of not only IRS-2 but also insulin receptor and IGF-1 receptor suppresses Aβ accumulation in AD mouse models, suggesting that reduced insulin signaling may exert an anti-amyloid effect. Using IRS-2 deficient mice, we are investigating the molecular mechanism of this effect.

References

1. Matsukawa K, Kukharsky MS, Park SK, Park S, Watanabe N, Iwatsubo T, Hashimoto T, Liebman SW, Shelkovnikova TA. Long non-coding RNA NEAT1_1 ameliorates TDP-43 toxicity in in vivo models of TDP-43 proteinopathy. ***RNA Biol***, 2021; 18(11): 1546–1554
2. Ochiai T, Nagayama T, Matsui K, Amano K, Sano T, Wakabayashi T, Iwatsubo T. Tauroursodeoxycholic Acid Attenuates Diet-Induced and Age-Related Peripheral Endoplasmic Reticulum Stress and Cerebral Amyloid Pathology in a Mouse Model of Alzheimer's Disease. ***J Prev Alzheimer Dis***, 2021; 8(4):483-494
3. Ochiai T, Sano T, Nagayama T, Kubota N, Kadowaki T, Wakabayashi T, Iwatsubo T. Differential involvement of insulin receptor substrate (IRS)-1 and IRS-2 in brain insulin signaling is associated with the effects on amyloid pathology in a mouse model of Alzheimer's disease. ***Neurobiol Dis***, 2021; 159:105510

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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 the two other staff members, Taisuke Jo and Nobuaki Michihata. Hayato Yamana was promoted to Project Lecturer in 2021.

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 armamentarium.

The followings are examples of studies conducted in 2020.

1) Sodium-containing versus sodium-trace preparations of IVIG for children with Kawasaki disease in the acute phase. (Eur J Pediatr. 2021 Nov;180: 3279–86.)

Objective: Kawasaki disease (KD) is an acute systemic vasculitis that most commonly causes acquired cardiac disease in children in developed countries. The most highly recommended treatment for KD is 2 g/kg intravenous immunoglobulin (IVIG). There are two types of IVIG, sodium-containing (high-Na) and sodium-trace (low-Na) preparations. However, few studies have compared the effects of these two preparations for superiority. The purpose of this study was to compare outcomes between high and low-Na IVIG preparations in KD children using a national inpatient database in Japan.

Methods: We used the Diagnostic Procedure Combination database to identify KD patients treated with IVIG between 2010 and 2017. We identified those receiving high and low-Na preparations of IVIG as an initial treatment. Outcomes included proportion of coronary artery abnormalities (CAA), IVIG resistance, adverse effects, length of stay, and medical cost. Propensity score-matched analyses were conducted to compare the outcomes between the two groups. Instrumental variable analyses were performed to confirm the results.

Results: We identified 42,345 patients with KD. There were significant differences in proportions of CAA (2.8% vs. 3.2%; p = 0.031) and IVIG resistance (17% vs. 18%, p = 0.001) between the two groups. However, there were no significant differences in length of stay or medical cost. The instrumental variable analysis confirmed the same results as the propensity score analysis.

Conclusion: The present study suggests that high-Na IVIG is potentially effective for reducing the proportion of CAA in KD patients. Prospective studies are warranted to confirm the effectiveness observed in this study

2) Association between maoto use and hospitalization for seasonal influenza in a nonelderly cohort in Japan. (Intern Med 2021;60:3401-8.)

Objective: Maoto is a traditional Japanese Kampo formula used to treat influenza. However, clinical evidence for maoto has been limited to small-scale studies of its effect in alleviating symptoms. The present study evaluated whether or not the addition of maoto to a neuraminidase inhibitor was associated with a reduction in hospitalization following influenza.

Methods: Using the JMDC Claims Database, we identified outpatients <60 years old who were diagnosed with influenza by an antigen test from September 2013 to August 2018. One-to-five propensity score matching was conducted between patients who received maoto in addition to a neuraminidase inhibitor and those who received a neuraminidase inhibitor alone. Hospitalization within seven days of the influenza diagnosis was compared in the matched groups using the Mantel-Haenszel test.

Results: We identified 1.79 million cases of influenza from the database in the 5-year study period. Maoto was prescribed for 3.9% of the 1.67 million cases receiving a neuraminidase inhibitor. In the 64,613 propensity score-matched groups of patients, the 7-day hospitalization rate was 0.116% (n = 75) for patients with maoto and 0.122% (n = 394) for patients without maoto. The difference between these treatment groups was nonsignificant (common odds ratio, 0.95; 95% confidence interval, 0.74 to 1.22; p = 0.695).

Conclusion: The addition of maoto to a neuraminidase inhibitor was not associated with a decrease in hospitalization among nonelderly patients with influenza. Further research is necessary to clarify the indication and efficacy of maoto.

3) Prognosis of patients with liver cirrhosis: a multicenter retrospective observational study. (Hepatol Res 2021;51:1196-206.)

Aim:Despite advances in the management of liver diseases and changes in the etiology of cirrhosis, few studies have updated the prognosis of cirrhosis. This study aimed to clarify the recent prognosis of cirrhosis and identify risk factors for death.

Methods: In this retrospective observational study by the Hepatic Disease Network of the National Hospital Organization in Japan, chart reviews were performed to follow patients with cirrhosis beginning in 2011.

We conducted Kaplan–Meier survival time analyses stratified by Child–Pugh classification and albumin-bilirubin grade. Cox regression analysis was used to identify risk factors for death.

Results: We identified 444 eligible patients from 25 hospitals, including 303 (68%), 110 (25%), and 31 (7%) patients with Child–Pugh classes A, B, and C, respectively. Hepatitis C virus infection was the cause of cirrhosis for 63% of the patients. The 1-year and 5-year cumulative survival rates of patients with Child–Pugh classes A, B, and C were 90% and 61%, 78% and 42%, and 65% and 25%, respectively. The 1-year and 5-year cumulative survival rates of patients with albumin-bilirubin grades 1, 2, and 3 were 98% and 80%, 91% and 56%, and 58% and 23%, respectively. Cirrhosis classification (Child–Pugh and albumin-bilirubin), age, liver cancer, and untreated esophageal varices were associated with increased hazard of death.

Conclusions: Little improvement was observed in the prognosis of cirrhosis compared with previous reports, and the prognosis of Child–Pugh class C cirrhosis remained poor. Untreated esophageal varices were identified as a risk factor for death.

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

1. 1. Ando T, Kawashima M, Jo T, Yasunaga H, Nagase T. The authors reply. *Crit Care Med* 2021; 49: e466-e467.
2. Awano N, Jo T, Yasunaga H, Inomata M, Kuse N, Tone M, Morita K, Matsui H, Fushimi K, Nagase T, Izumo T. Body mass index and in-hospital mortality in patients with acute exacerbation of idiopathic pulmonary fibrosis. *ERJ Open Res* 2021; 7.
3. Fukui A, Kaneko H, Okada A, Yano Y, Itoh H, Matsuoka S, Morita K, Kiriyama 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. Semi-quantitative assessed proteinuria and risk of heart failure: Analysis of a nationwide epidemiological database. *Nephrol Dial Transplant* 2021.
4. Hashimoto Y, Michihata N, Yamana H, Shigemi D, Morita K, Matsui H, Yasunaga H, Aihara M. Intraocular pressure-lowering medications during pregnancy and risk of neonatal adverse outcomes: a propensity score analysis using a large database. Br J Ophthalmol 2021;105: 1390-4.
5. Hatachi T, Michihata N, Inata Y, Takeuchi M, Matsui H, Fushimi K, Yasunaga H. Prognostic Factors Among Children With Acute Encephalitis/Encephalopathy Associated With Viral and Other Pathogens. Clin Infect Dis. 2021 Jul 1;73:76–82.
6. Honda C, Naruse T, Yamana H, Yamamoto-Mitani N. Infant injury prevention education for pregnant women attending antenatal class: a quasi-experimental study. Int J Environ Res Public Health 2021;18:9393.
7. Honda A, Michihata N, Iizuka Y, Mieda T, Takasawa E, Ishiwata S, Matsui H, Fushimi K, Yasunaga H, Chikuda H. Clinical features and early post-operative complications of isolated C2 odontoid fractures: a retrospective analysis using a national inpatient database in Japan. Eur Spine J. 2021 May
8. Ikawa F, Isobe N, Michihata N, Oya S, Ohata K, Saito K, Yoshida K, Fushimi K, Yasunaga H, Tominaga T, Kurisu K. In-Hospital Complications After Surgery in Elderly Patients with Asymptomatic or Minor Symptom Meningioma: A Nationwide Registry Study. World Neurosurg. 2021 Apr;148:e459–70.
9. Isago H, Mitani A, Kohno S, Nagoshi S, Ishimori T, Saito M, Tamiya H, Miyashita N, Ishii T, Matsuzaki H, Yatomi Y, Nagase T, Jo T. The Japanese Herbal (Kampo) Medicine Hochuekkito Attenuates Lung Inflammation in Lung Emphysema. *Biol Pharm Bull* 2021; 44: 39-45.
10. Itoh H, Kaneko H, Fujiu K, Kiriyama H, Morita K, Kamon T, Michihata N, Jo T, Takeda N, Morita H, Yasunaga H, Komuro I. Risk Factors and Lifestyles in the Development of Atrial Fibrillation Among Individuals Aged 20-39 Years. *Am J Cardiol* 2021; 155: 40-44.

11. Itoh H, Kaneko H, Kiriyama H, Kamon T, Fujiu K, Morita K, Michihata N, Jo T, Takeda N, Morita H, Yasunaga H, Komuro I. Metabolically Healthy Obesity and the Risk of Cardiovascular Disease in the General Population- Analysis of a Nationwide Epidemiological Database. *Circ J* 2021; 85: 914-920.
12. Itoh H, Kaneko H, Kiriyama H, Kamon T, Fujiu K, Morita K, Yotsumoto H, Michihata N, Jo T, Takeda N, Morita H, Yasunaga H, Komuro I. Reverse J-shaped relationship between body mass index and in-hospital mortality of patients hospitalized for heart failure in Japan. *Heart Vessels* 2021; 36: 383-392.
13. Itoh H, Kaneko H, Okada A, Yano Y, Morita K, Seki H, Kiriyama H, Kamon T, Fujiu K, Matsuoka S, Nakamura S, Michihata N, Jo T, Takeda N, Morita H, Nishiyama A, Node K, Yasunaga H, Komuro I. Fasting Plasma Glucose and Incident Colorectal Cancer: Analysis of a Nationwide Epidemiological Database. *J Clin Endocrinol Metab* 2021.
14. Jimba T, Kaneko H, Yano Y, Itoh H, Yotsumoto H, Seki H, Morita K, Kiriyama H, Kamon T, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Nishiyama A, Node K, Yasunaga H, Komuro I. Relation of the Metabolic Syndrome to Incident Colorectal Cancer in Young Adults Aged 20 to 49 Years. *Am J Cardiol* 2021; 158: 132-138.
15. Jo T, Michihata N, Yamana H, Morita K, Ishimaru M, Yamauchci Y, Hasegawa W, Urushiyama H, Uda K, Matsui H, Fushimi K, Yasunaga H, Nagase T. Risk of drug-induced interstitial lung disease in hospitalised patients: a nested case–control study. Thorax 2021;76: 1193-9.
16. Kamon T, Kaneko H, Itoh H, Okada A, Matsuoka S, Kiriyama H, Fujiu K, Morita K, Michihata N, Jo T, Takeda N, Morita H, Nakamura S, Node K, Yasunaga H, Komuro I. Sex Difference in the Association between Lipid Profile and Incident Cardiovascular Disease among Young Adults. J Atheroscler Thromb. 2022 Jan;
17. Kaneko H, Itoh H, Morita K, Sugimoto T, Konishi M, Kamiya K, Kiriyama H, Kamon T, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Yasunaga H, Komuro I. Early Initiation of Feeding and In-Hospital Outcomes in Patients Hospitalized for Acute Heart Failure. Am J Cardiol. 2021 Apr 15;145:85–90.
18. Kaneko H, Itoh H, Yotsumoto H, Kiriyama H, Kamon T, Fujiu K, Morita K, Kashiwabara K, Michihata N, Jo T, Morita H, Yasunaga H, Komuro I. Cardiovascular Health Metrics of 87,160 Couples: Analysis of a Nationwide Epidemiological Database. J Atheroscler Thromb. 2021 May;28:535–43.
19. Kaneko H, Yano Y, Itoh H, Morita K, Kiriyama H, Kamon T, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Node K, Carey RM, Lima JAC, Oparil S, Yasunaga H, Komuro I. Association of Blood Pressure Classification Using the 2017 American College of Cardiology/American Heart Association Blood Pressure Guideline With Risk of Heart Failure and Atrial Fibrillation. Circulation. 2021 Jun;143:2244–53.
20. Kaneko H, Yano Y, Itoh H, Morita K, Kiriyama H, Kamon T, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Nishiyama A, Node K, Bakris G, Miura K, Muntner P, Viera AJ, Oparil S, Lloyd-Jones DM, Yasunaga H, Komuro I. Untreated Hypertension and Subsequent Incidence of Colorectal Cancer: Analysis of a Nationwide Epidemiological Database. J Am Heart Assoc. 2021 Nov 16;10:e022479.
21. Katsuki R, Jo T, Yasunaga H, Ishimaru M, Sakamoto T. Outcomes of self-expandable metal stent as bridge to surgery versus emergency surgery for left-sided obstructing colon cancer: A retrospective cohort study. *Am J Surg* 2021; 221: 168-173.
22. Kawata M, Jo T, Taketomi S, Inui H, Yamagami R, Matsui H, Fushimi K, Yasunaga H, Tanaka S. Type of bone graft and primary diagnosis were associated with nosocomial surgical site infection after high tibial osteotomy: analysis of a national database. *Knee Surg Sports Traumatol Arthrosc* 2021; 29: 429-436.
23. Kim H, Cheng SH, Yamana H, Lee S, Yoon NH, Lin YC, Fushimi K, Yasunaga H. Variations in hip fracture inpatient care in Japan, Korea, and Taiwan: an analysis of health administrative data. BMC Health Serv Res 2021;21:694.

24. Kiriyama H, Kaneko H, Itoh H, Kamon T, Morita K, Jo T, Fujiu K, Daimon M, Takeda N, Morita H, Yasunaga H, Komuro I. Surgical treatment for infective endocarditis in the ageing society: a nationwide retrospective study in Japan. Open Heart 2021; 8.
25. Kobayashi K, Jo T, Mimura W, Suzukawa M, Ohshima N, Tanaka G, Akazawa M, Matsui H, Fushimi K, Yasunaga H, Nagase T, Nagai H. Interrupted time-series analyses of routine vaccination program for elderly pneumonia patients in Japan; an ecological study using aggregated nationwide inpatient data. *Hum Vaccin Immunother* 2021; 17: 2661-2669.
26. Konishi T, Fujiogi M, Michihata N, Kumazawa R, Matsui H, Fushimi K, Tanabe M, Seto Y, Yasunaga H. Outcomes of Nonoperative Treatment for Gastroduodenal Ulcer Perforation: a Nationwide Study of 14,918 Inpatients in Japan. J Gastrointest Surg. 2021 Apr.
27. Konishi T, Fujiogi M, Michihata N, Morita K, Matsui H, Fushimi K, Tanabe M, Seto Y, Yasunaga H. Comparisons of postoperative outcomes after breast cancer surgery in patients with and without renal replacement therapy: a matched-pair cohort study using a Japanese nationwide inpatient database. Breast Cancer. 2021 Apr.
28. Konishi T, Fujiogi M, Michihata N, Morita K, Matsui H, Fushimi K, Tanabe M, Seto Y, Yasunaga H. Comparison of short-term surgical outcomes between men and women with breast cancer: a retrospective study using nationwide inpatient data in Japan. Breast Cancer Res Treat. 2021 Apr;186:731–9.
29. Konishi T, Fujiogi M, Michihata N, Morita K, Matsui H, Fushimi K, Tanabe M, Seto Y, Yasunaga H. Comparing outcomes of nonoperative treatment for adhesive small bowel obstruction with and without antibiotics. J Infect Chemother. 2021 May;27:690–5.
30. 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: e210081.
31. Kurakawa KI, Okada A, Manaka K, Konishi T, Jo T, Ono S, Uda K, Michihata N, Matsui H, Fushimi K, Yamaguchi S, Yamauchi T, Nangaku M, Yasunaga H, Kadowaki T. Clinical Characteristics and Incidences of Benign and Malignant Insulinoma Using a National Inpatient Database in Japan. *J Clin Endocrinol Metab* 2021; 106: 3477-3486.
32. Matsuda K, Ise M, Shimura A, Honda A, Masamoto Y, Jo T, Yasunaga H, Kurokawa M. Use of wide-spectrum antimicrobials with blood culture tests during chemotherapy as an accurate marker of febrile neutropenia in the DPC database: A validation study. *J Infect Chemother* 2021; 27: 1541-1542.
33. Matsuda K, Jo T, Miyauchi M, Toyama K, Nakazaki K, Matsui H, Fushimi K, Yasunaga H, Kurokawa M. Difference of preventing effects of G-CSF according to age in patients with malignant lymphoma: A nation-wide analysis in Japan. *J Infect Chemother* 2021; 27: 1151-1155.
34. Matsuda K, Jo T, Toyama K, Nakazaki K, Matsui H, Fushimi K, Yasunaga H. Efficacy of recombinant human soluble thrombomodulin in induction therapy for acute promyelocytic leukemia. *Thromb Res* 2021; 202: 173-175.
35. Matsuda K, Jo T, Toyama K, Nakazaki K, Matsui H, Fushimi K, Yasunaga H, Kurokawa M. Risk factors for early in-hospital death in patients who developed coagulopathy during induction therapy for acute promyelocytic leukemia: a nationwide analysis in Japan. *Ann Hematol* 2021; 100: 2613-2619.
36. Matsuoka S, Kaneko H, Yano Y, Itoh H, Fukui A, Morita K, Kiriyama H, Kamon T, Fujiu K, Seki H, Michihata N, Jo T, Takeda N, Morita H, Nakamura S, Yokoo T, Nishiyama A, Node K, Yasunaga H, Komuro I. Association Between Blood Pressure Classification Using the 2017 ACC/AHA Blood Pressure Guideline and Retinal Atherosclerosis. Am J Hypertens. 2021 May; hpab074.
37. 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. Incorporation of Retinal Arteriolosclerosis into Risk Stratification of Blood Pressure Category According to the 2017 ACC/AHA Blood Pressure Guideline. J Atheroscler Thromb. 2021 Dec

38. Miyano S, Michihata N, Sada KE, Uda K, Matsui H, Fushimi K, Nangaku M, Yasunaga H. Comparison of fracture risk between proton pump inhibitors and histamine-2 receptor antagonists in ANCA-associated vasculitis patients: a nested case-control study. Rheumatology (Oxford). 2021 Apr 6;60:1717–23.
39. Mongkonchoo K, Yamana H, Aso S, Machida M, Takasaki Y, Jo T, Yasunaga H, Chongsuvivatwong V, Liabsuetrakul T. Prediction of outpatient visits and expenditure under the Universal Coverage Scheme in Bangkok using subscriber's attributes: a random forest analysis. Public Health in Practice 2021;2: 100190.
40. 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 Jan;5:93–8.
41. Ohbe H, Sasabuchi Y, Yamana H, Matsui H, Yasunaga H. Intensive care unit versus high-dependency care unit for mechanically ventilated patients with pneumonia: a nationwide comparative effectiveness study. The Lancet Regional Health - Western Pacific 2021;13: 100185.
42. Ohbe H, Yamana H, Matsui H, Yasunaga H. Development and validation of a procedure-based organ failure assessment model for patients in the intensive care unit: an administrative database study. Acute Med Surg 2021;8:e719.
43. Okada A, Yamana H, Morita K, Sato Y, Yamaguchi S, Kurakawa KI, Michihata N, Matsui H, Fushimi K, Nangaku M, Yamauchi T, Yasunaga H, Kadowaki T. Potassium concentration in initial fluid therapy and in-hospital mortality of patients with diabetic ketoacidosis. J Clin Endocrinol Metab 2021;105: e2162-75.
44. Okada A, Ono S, Yamaguchi S, Yamana H, Kurakawa KI, Michihata N, Matsui H, Nangaku M, Yamauchi T, Yasunaga H, Kadowaki T. Association between nutritional guidance or ophthalmological examination and discontinuation of physician visits in patients with newly diagnosed diabetes: a retrospective cohort study using a nationwide database. J Diabetes Investig 2021;12:1619-31.
45. Okubo Y, Michihata N, Morisaki N, Yoshida K, Matsui H, Fushimi K, Yasunaga H. Effects of Glucocorticoids on Hospitalized Children With Anaphylaxis. Pediatr Emerg Care. 2021 May;37: 255–9.
46. Ono S, Ishimaru M, Ida Y, Yamana H, Ono Y, Hoshi K, Yasunaga H. Validity of diagnoses and procedures in Japanese dental claims data. BMC Health Serv Res 2021;21:1116.
47. Sakamoto Y, Yamauchi Y, Jo T, Michihata N, Hasegawa W, Takeshima H, Matsui H, Fushimi K, Yasunaga H, Nagase T. In-hospital mortality associated with community-acquired pneumonia due to methicillin-resistant Staphylococcus aureus: a matched-pair cohort study. *BMC Pulm Med* 2021; 21: 345.
48. 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 2021;26:666-71.
49. Seki H, Kaneko H, Morita H, Itoh H, Morita K, Matsuoka S, Kiriyama H, Kamon T, Fujiu K, Michihata N, Jo T, Takeda N, Yano Y, Nakamura S, Node K, Yasunaga H, Komuro I. Relation of Serum Uric Acid and Cardiovascular Events in Young Adults Aged 20-49 Years. Am J Cardiol. 2021 Aug;152:150–7.
50. Shigemi D, Morishima T, Yamana H, Yasunaga H, Miyashiro I. Validity of initial cancer diagnoses in the Diagnosis Procedure Combination data in Japan. Cancer Epidemiol 2021;74:102016.
51. Shigemi D, Hashimoto Y, Michihata N, Yasunaga H. Effect of Japanese herbal Kampo medicines

on live birth rate in women with recurrent pregnancy loss. Int J Gynaecol Obstet. 2021 Jun; 153:489–95.

52. Shinozaki N, Morita K, Matsui H, Jo T, Yasunaga H. Semisolid vs Liquid Nutrients and 30-Day Readmission in Gastrostomy Tube-Fed Patients: A Propensity-Matched Analysis. *JPEN J Parenter Enteral Nutr* 2021; 45: 720-728.
53. Shiozawa M, Kaneko H, Itoh H, Morita K, Okada A, Matsuoka S, Kiriyama H, Kamon T, Fujiu K, Michihata N, Jo T, Takeda N, Morita H, Nakamura S, Node K, Yasunaga H, Komuro I. Association of Body Mass Index with Ischemic and Hemorrhagic Stroke. *Nutrients* 2021; 13.
54. Suzuki T, Michihata N, Aso S, Yoshikawa T, Saito K, Matsui H, Fushimi K, Yasunaga H. Sodium-containing versus sodium-trace preparations of IVIG for children with Kawasaki disease in the acute phase. Eur J Pediatr. 2021 Nov;180:3279–86.
55. 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;53:240–8.
56. Takano A, Yamana H, Ono S, Matsui H, Yasunaga H. Outpatient treatment following alcohol screening at health checkups and change in drinking patterns among excessive drinkers with lifestyle-related diseases. Prev Med Rep 2021;24:101549.
57. Tamiya H, Mitani A, Isago H, Ishimori T, Saito M, Jo T, Tanaka G, Yanagimoto S, Nagase T. Measurement of chest wall motion using a motion capture system with the one-pitch phase analysis method. *Sci Rep* 2021; 11: 21497.
58. Tanaka G, Jo T, Tamiya H, Sakamoto Y, Hasegawa W, Matsui H, Fushimi K, Yasunaga H, Nagase T. Factors affecting in-hospital mortality of non-tuberculous mycobacterial pulmonary disease. *BMC Infect Dis* 2021; 21: 698.
59. Urushiyama H, Jo T, Hasegawa W, Ando T, Sakamoto Y, Uda K, Matsui H, Fushimi K, Yasunaga H, Nagase T. Preoperative use of pirfenidone and reduced risk of postoperative severe respiratory complications in patients with idiopathic pulmonary fibrosis: Propensity score-matched analysis using a nationwide database in Japan. *Respirology* 2021; 26: 590-596.
60. Ueno K, Kamiya K, Kaneko H, Okada A, Itoh H, Fujiu 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 Mar;9:97.
61. Ugata Y, Michihata N, Matsui H, Fushimi K, Yasunaga H. Impact of proton pump inhibitors on mortality and severe esophageal injury after catheter ablation for atrial fibrillation: a nationwide retrospective study using propensity score matching. Heart Vessels. 2021 Apr.
62. Yamana H, Iba A, Tomio J, Ono S, Jo T, Yasunaga H. Treatment of latent tuberculosis infection in patients receiving biologic agents. J Infect Chemother 2021;27:243-9.
63. Yamana H, Ono S, Michihata N, Jo T, Yasunaga H. Association between maoto use and hospitalization for seasonal influenza in a nonelderly cohort in Japan. Intern Med 2021;60: 3401-8.
64. Yamana H, Imai S, Yamasaki K, Horiguchi H, Ario K, Komatsu T, Sugimoto R, Katsushima S, Naganuma A, Mano Y, Yamashita T, Kamitsukasa H, Tsuruta S, Jo T, Yasunaga H, Fushimi K, Yatsuhashi H. Prognosis of patients with liver cirrhosis: a multi-center retrospective observational study. Hepatol Res 2021;51:1196-206.
65. Yagi Y, Takahashi Y, Ogata Y, Yamana H, Kumakura Y, Ichihashi K, Kasai K, Kondo S. Oral corticosteroid dosage and clinical presentation of psychiatric conditions after steroid use: a consultation-liaison psychiatry service's experience. Neuropsychopharmacol Rep 2021;41:471-5.
66. Yasui H, Michihata N, Matsui H, Fushimi K, Iwase S, Yoshiuchi K, Sakata Y, Yasunaga H. Association between ambulance use and

hospitalization costs among heart failure patients. Heart Vessels. 2021 May;36:654–8.
67. Yokoyama A, Sakamoto Y, Jo T, Urushiyama H, Tamiya H, Tanaka G, Matsui H, Fushimi K, Yasunaga H, Nagase T. Pulmonary disease as a risk factor for transfusion-related acute lung injury. *ERJ Open Res* 2021; 7.
68. Yoshii E, Yamana H, Ono S, Matsui H, Yasunaga H. Association between allergic or autoimmune diseases and incidence of endometriosis: a nested case-control study using a health insurance claims database. Am J Reprod Immunol 2021;86: e13486.
69. Yoshihara S, Yamana H, Akahane M, Kishimoto M, Nishioka Y, Noda T, Matsui H, Fushimi K, Yasunaga H, Kasahara K, Imamura T. Association between prophylactic antibiotic use for transarterial chemoembolization and occurrence of liver abscess: a retrospective cohort study. Clin Microbiol Infect 2021;27:1514.e5-10.

Books

1. Michihata N, Aso S, Fujiogi M. Medical Statistics, a book to learn the basics using Stata while analyzing data. Yodosha; 2021.

Division of Chronic Kidney Disease (CKD) Pathophysiology

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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, glycative 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),
  20K17243 (to **Hiroshi Maekawa**, The elucidation of pathophysiology of cGAS-STING pathway in AKI-to-CKD transition).
- 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)
- Nipro Co. Ltd, (to **Reiko Inagi**, Collaborative study on metabolome of serum exosome in HD patients)
- Astellas Foundation for Research on Metabolic Disorders, Research Grant, (to **Reiko Inagi**, Pathophysiological role for organelle crosstalk based on primary cilia)
- MSD Life Science Foundation, Public Interest Incorporated Foundation, Research Grant (to **Sho Hasegawa**, Pathophysiological role of ER-mitochondria crosstalk in diabetic kidney disease)
- The Cell Science Research Foundation (to **Sho Hasegawa**, Elucidation of the pathogenesis of ER-mitochondria crosstalk in diabetic kidney disease)
- Takeda Science Foundation, Medical Research Grant (to **Sho Hasegawa**, Elucidation of the pathophysiological role of ER-mitochondria contact site in diabetic kidney disease)
- The Ichiro Kanehara Foundation for the Promotion of Medical Sciences and Medical care (to **Sho Hasegawa**, Study on the pathophysiological effect of peripheral nerve remodeling in chronic kidney disease)

Awards

Prof. Reiko Inagi received the Kidney International 2020 Reviewer-Of-The-Year Award from the International Society of Nephrology.

Prof. Reiko Inagi received the Kidney International 2021 Reviewer-Of-The-Year Award from the International Society of Nephrology.

Dr. Sho Hasegawa received the ISN-KI Early-Career Researcher Award from the International Society of Nephrology.

Dr. Sho Hasegawa received the Best Abstract Award at the 4th Annual Meeting of the Japanese Society of Uremic toxin Reserach.

Dr. Sho Hasegawa received the ISN-KI Editorial Fellowship in Basic and Translational Nephrology in the International Society of Medicine (2021-2023).

Dr. Kentaro Yoshioka received the President Award at the 11th Annual Meeting of the Japanese Society of Pathophysiology in Kidney Failure.

References

1. Okpechi IG, Caskey FJ, Gaipov A, Tannor EK, Hamonic LN, Ashuntantang G, Donner JA, Figueiredo A, Inagi R, Madero M, Malik C, Moorthy M, Pecoits-Filho R, Tesar V, Levin A, Jha V. Assessing the impact of screening, early identification and intervention programmes for chronic kidney disease: protocol for a scoping review. **BMJ Open.** 2021 Dec 16;11(12): e053857. doi: 10.1136/bmjopen-2021-053857.
2. Hasegawa S, Okada A, Aso S, Kumazawa R, Matsui H, Fushimi K, Yasunaga H, Nangaku M. Association Between Diabetes and Major Bleeding Complications of Renal Biopsy. **Kidney Int Rep.** 2021 Nov 25; 7(2): 232-240. doi: 10.1016/j.ekir.2021.11.013.
3. Hasegawa S, Inagi R. The subtle long-lasting burden of mitochondrial DNA variants. **Nat Rev Nephrol.** 2021 Oct 18. doi: 10.1038/s41581-021-00500-9.
4. Fujii R, Hasegawa S, Maekawa H, Inoue T, Yoshioka K, Uni R, Ikeda Y, Nangaku M, Inagi R. Decreased IFT88 expression with primary cilia shortening causes mitochondrial dysfunction in cisplatin-induced tubular injury. **Am J Physiol Renal Physiol.** 2021 Sep 1;321(3):F278-F292. doi: 10.1152/ajprenal.00673.2020.
5. Doi K, Kimura H, Wada T, Tanaka T, Hiromura K, Saleem MA, Inagi R, Nangaku M, Fujii T. A novel method for successful induction of interdigitating process formation in conditionally immortalized podocytes from mice, rats, and humans. **Biochem Biophys Res Commun.** 2021 Sep 17; 570:47-52. doi: 10.1016/j.bbrc.2021.07.029.
6. Sakashita M, Tanaka T, Inagi R. Metabolic Changes and Oxidative Stress in Diabetic Kidney Disease. **Antioxidants (Basel).** 2021 Jul 19; 10(7):1143. doi: 10.3390/antiox10071143.
7. Hasegawa S, Inagi R. Harnessing Metabolomics to Describe the Pathophysiology Underlying Progression in Diabetic Kidney Disease. **Curr Diab Rep.** 2021 May 11;21(7):21. doi: 10.1007/s11892-021-01390-8
8. Higashihara T, Nishi H, Takemura K, Watanabe H, Maruyama T, Inagi R, Tanaka T, Nangaku M. β2-adrenergic receptor agonist counteracts skeletal muscle atrophy and oxidative stress in uremic mice. **Sci Rep.** 2021 Apr 28;11(1):9130. doi:10.1038/s41598-021-88438-7.
9. Muso E, Sakai S, Ogura Y, Yukawa S, Nishizawa Y, Yorioka N, Saito T, Mune M, Sugiyama S, Iino Y, Hirano T, Hattori M, Watanabe T, Yokoyama H, Sato H, Uchida S, Wada T, Shoji T, Oda H, Mori K, Kimura H, Ito O, Nishiyama A, Maruyama S, Inagi R, Fujimoto S, Tsukamoto T, Suzuki Y, Honda H, Babazono T, Tsuruya K, Yuzawa Y. Favorable therapeutic efficacy of low-density lipoprotein apheresis for nephrotic syndrome with impaired renal function. **Ther Apher Dial.** 2022 Feb;26(1):220-228. doi: 10.1111/1744-9987.13694.
10. Hasegawa S, Inoue T, Nakamura Y, Fukaya D, Uni R, Wu CH, Fujii R, Peerapanyasut W, Taguchi A, Kohro T, Yamada S, Katagiri M, Ko T, Nomura S, Nakanishi Ozeki A, Susaki EA, Ueda HR, Akimitsu N, Wada Y, Komuro I, Nangaku M, Inagi R. Activation of Sympathetic Signaling in Macrophages Blocks Systemic Inflammation and Protects against Renal Ischemia-Reperfusion Injury. **J Am Soc Nephrol.**

2021 Apr 19: ASN.2020121723. doi: 10.1681/ASN.2020121723

11. Inagi R. Organelle stress and glycation in kidney disease. **Glycoconj J.** 2021 Jun;38(3):341-346. doi: 10.1007/s10719-021-09989-5.

Department of Retinal Biology and Pathology

Project Professor

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Project Assistant Professor

Toshiro Iwagawa, Ph.D

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. 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 started to work 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, and how to build the inflammatory environment within retina is an important issue to be solved. There are several retinal immunocompetent cells, and we have particular interests with the microglia. In the new laboratory, we expanded our focus from retina to retina and sclera with particular interest with blood vessel. Therefore, not only retinitis pigmentosa, various vessel related diseases such as ocular complications of diabetic mellitus are our research targets. Microglia and inflammatory environment in retina must play pivotal roles for the vessel related ocular disease, and we established several assay system related to this point both in in vitro and in vivo.

The laboratory aimed to bridge the basic research team and the clinical team. We have regular discussion occasion 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, 4 master course students) moved to Hongo campus from IMSUT when our current laboratory started. All of students have their own project, and in 2021, we submitted two 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.

We also participate to train Ph.D candidate students of the ophthalmology department by teaching principles of experimental techniques and discussing research data.

Research activities

Summary of the research: Mouse and human iPS cells are two major models used in our research.

Technically, we had been employing molecular biology,and biochemistry, but introduced the LC-MS based membrane lipid analysis and the proteome in collaboration with the experts. Ophthalmological techniques also facilitate to make our research activities deepen with broad spectrum. Details of some of specific projects are as follows.

＊Analysis of membrane phospholipid dynamism in healthy and pathological retinas.

Membrane phospholipids play pivotal roles in various cellular processes, and their levels are tightly regulated. In the retina, phospholipids had been scrutinized because of their distinct composition and requirement in visual transduction. However, how lipid composition changes during retinal development remains unclear. Here, we used liquid chromatography-mass spectrometry (LC-MS) to assess the dynamic changes in the levels of two main glycerophospholipids, phosphatidylcholine (PC) and phosphatidylethanolamine (PE), in the developing mouse retina under physiological and pathological conditions. The total levels of PC and PE increased during retinal development, and individual lipid species exhibited distinct level changes. The amount of very-long-chain PC and PE increased dramatically in the late stages of retinal development. The mRNA levels of Elovl2 and Elovl4, genes encoding enzymes essential for the synthesis of very-long-chain polyunsaturated fatty acids, increased in developing photoreceptors. Cell sorting based on CD73 expression followed by LC-MS revealed distinct changes in PC and PE levels in CD73-positive rod photoreceptors and CD73-negative retinal cells. Finally, using the $NaIO_3$-induced photoreceptor degeneration model, we identified photoreceptor-specific changes in PC and PE levels from 1 day after $NaIO_3$ administration, before the outer segment of photoreceptors displayed morphological impairment. In conclusion, our findings provide insight into the dynamic changes in PC and PE levels in the developing and adult mouse retina under physiological and pathological conditions. Furthermore, we provide evidence that cell sorting followed by LC-MS is a promising approach for investigating the relevance of lipid homeostasis in the function of different retinal cell types.

＊Roles of histone H3K4 methyltranferase Sed1a for retinal development

During retinal development, retinal progenitor cells (RPCs) proliferate and differentiate into six types of neurons and one type of glial cell. The temporal order of the production of each retinal cell is known to be highly regulated and conserved among species. The molecular mechanisms by which cell fate is determined and maturation is accomplished have been intensively investigated, and much attention has been paid to the roles of transcription factors in the retinal development. Moreover, the contributions of epigenetic modifications, such as DNA methylation and histone modifications, to the retinal development are becoming more clear. We have been studying epigenetic histone modifications during retinal development and, with others, found that histone H3 methylation at lysine 4 (H3K4) and 27 (H3K27), which facilitates transcriptional gene activation and repression, respectively, was highly specific to retinal cell type. Additionally, analyses of knockout mice have revealed the functions of enzymes involved in these processes, especially H3K27 methylation. At least nine histone lysine methyltransferases and five histone lysine demethylases have been reported to be involved in H3K4 methylation. We found high levels of H3K4me3 in photoreceptor-related genes in rod photoreceptor lineage. However, involvement of H3K4 methylation in early retinal development is not well-documented. This time, we focus on Setd1a, which is the methyltransferase specific to H3K4. H3K4me3 has been reported to regulate rod photoreceptor differentiation; however, the roles H3K4me3 plays in retinal progenitor cell (RPC) proliferation and differentiation during early retinal development remain unclear. Using an in vitro retinal explant culture system, we suppressed the expression of Setd1a by introducing shSetd1a. We examined the expression level and H3K4me3 level of genes by RNA Sequencing and ChIP assay, respectively. We found that Setd1a depletion resulted in increased apoptosis and proliferation failure in late RPCs. Expression of wild-type SETD1A, but not SETD1A that lacked the catalytic SET domain, reversed the shSetd1a-induced phenotype. RNA Sequencing revealed that proliferation-related genes were downregulated upon shSetd1a expression. Based on publicly available

H3K4me3-ChIP sequencing data of retinal development, we identified Uhrf1 as a candidate target gene of Setd1a. Uhrf1 is multi-functional gene and recently paid attention since UHRF1 plays pivotal roles for carcinogenesis and DNA damage repair. The expression of shSetd1a led to a decrease in Uhrf1 transcript levels and reduced H3K4me3 levels at the Uhrf1 locus. Increased apoptosis and the suppression of proliferation in late RPCs were observed in retinal explants expressing shUhrf1, similar to the outcomes observed in shSetd1a-expressing retinas. The overexpression of UHRF1 did not rescue shSetd1a-induced apoptosis, but reversed the suppression of proliferation**.** These results indicate that Setd1a contributes to the survival and proliferation of retinal cells by regulating histone methylation, Setd1a regulates Uhrf1 expression, and these two molecules cooperate to regulate RPC survival and proliferation.

References

1. Kohno, H, Terauchi, R, Watanabe, S, Ichihara, K, Watanabe, T, Nishijima, E, Watanabe, A, Nakano, T. Effect of lecithin-bound iodine treatmen on inherited retinal degeneration in mice. TVST, 2021 10(13); 8
2. Nakamura, N, Honjo,, H, Yamagishi, R, Kurano, M, Yatomi, Y, Watanabe, S, Aihara, M. Neuroprotective Role of sphingolipid rheostat in Excitotoxic Retinal Ganglion Cell Death, Exp Eye Res. 2021 208: 108623
3. Deng, X, Iwagawa, T, Fukushima, M, Suzuki, Y, Watanabe, S. Setd1a plays pivotal roles for the survival and proliferation of retinal progenitors via histone modifications of Uhrf1, Invest. Ophthalmol. Vis. Sci. 2021 62(6), 1
4. Terauchi, R, Kohno, H, Watanabe, S. Saito, S, Watanabe, A, Nakano, T. Ccr2 suppression by minocycline in Cx3cr1/Ccr2-visualized inherited retinal Degeneration, PlosOne 2021 16: e0239108
5. Hamano, F, Kuribayashi, H, Iwagawa, T, Nagata, K, Shimizu, T, Shindou, T, Watanabe, S, Mapping of membrane lipids in the developing and adult mouse retina under physiological and pathological conditions using mass spectrometry. J. Biol. Chem. 2021 296, 100303

Department of Lipidomics

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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. This year marks the 20th year since the launch of the former donated laboratory for metabolomics.

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.

Lipid biomarker/lipid mediator discovery using animal models

Appling the latest lipidomics technologies to the analysis of specimens from the animal models for various diseases including metabolic disease, we are trying to discover novel lipid biomarkers. We also analyze various gene-deficient mice and transgenic mice to seek important lipid markers, lipid mediators, and lipid profiles.

Multiplex quantitation strategy for lipid mediators

Lipid mediators, including prostaglandins, leukotrienes, platelet-activating factor, and many other bioactive lipid metabolites are attracting great attention as disease-related or physiologically important molecules. Comprehensive analysis of known lipid mediators is a useful, unbiased method in disease mechanism studies, and the lipid mediator profile is a useful parameter that characterizes disease status as well. We have developed an original multiplex quantification method for trace amounts of lipid mediators 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 lipid mediator 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.

References

1. 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).
2. 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).
3. 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).
4. 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.
5. 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.
6. 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.
7. 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)
8. 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)
9. 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)
10. 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)
11. 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 Gα12/13-coupled receptor, LPA4 limits proper adipose tissue expansion and remodeling in diet-induced obesity. JCI Insight, 3, e97293 (2018) (First published December 20, 2018)
12. 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)
13. Hori T, Okuno T, Hirata K, Yamashita K, Kawano Y, Yamamoto M, Hato M, Nakamura M, Shimizu T, Yokomizo T, Miyano M, Yokoyama S. Na+-mimicking ligands stabilize the inactive state of leukotriene B4 receptor BLT1. Nat Chem Biol, 14, 262–269 (2018)
14. Valentine WV, Tokuoka SM, Hishikawa D, Kita Y, Shindou H, Shimizu T. Lysophosphatidic acid acyltransferase 3 incorporates docosahexaeneoic acid into skeletal muscle cell membranes and is upregulated by PPARδ activation. J Lipid Res, 59, 184-194 (2018)
15. Tabe S, Hikiji H, Ariyoshi W, Hashidate-Yoshida T, Shindou H, Shimizu T, Okinaga T, Seta Y, Tominaga K, Nishihara T. Lysophosphatidylcholine acyltransferase 4 is involved in chondrogenic differentiation of ATDC5 cells. Sci Rep, 7, 16701(2017)
16. Kimura H, Suzuki M, Konno S, Shindou H, Shimizu T, Nagase T, Miyazaki T, Nishimura M. Orchestrating role of apoptosis inhibitor of macrophage in the resolution of acute lung injury. J Immunol, 199, 3870-3882 (2017)
17. Iizuka-Hishikawa Y, Hishikawa D, Sasaki J, Takubo K, Goto M, Nagata K, Nakanishi H, Shindou H, Okamura T, Ito C, Toshimori K, Sasaki T, Shimizu T. Lysophosphatidic acid acyltransferase 3 tunes the membrane status of germ cells by incorporating docosahexaenoic acid during spermatogenesis. J Biol Chem, 292, 12065-12076 (2017)
18. Shindou H, Koso H, Sasaki J, Nakanishi H, Sagara H, Nakagawa MK, Takahashi Y, Hishikawa D, Iizuka-Hishikawa Y, Tokumasu F, Noguchi H, Watanabe S, Sasaki T, Shimizu T. Docosahexaenoic acid preserves visual function by maintaining correct disc morphology in retinal photoreceptor cells. J Biol Chem, 292, 12054-12064 (2017)
19. Takeda T, Komiya Y, Koga T, Ishida T, Ishii Y, Kikuta Y, Nakaya M, Kurose H, Yokomizo T, Shimizu T, Uchi H, Furue M, Yamada H. Dioxin-induced increase in leukotriene B4 biosynthesis through the aryl hydrocarbon receptor and its relevance to hepatotoxicity owing to neutrophil infiltration. J Biol Chem, 292. 10586-10599 (2017)
20. Shindou H, Shiraishi S, Tokuoka MS, Takahashi Y, Harayama T, Abe T, Bando K, Miyano K, Kita Y, Uezono Y, Shimizu T. Relief from neuropathic pain by blocking of platelet-activating factor-pain loop. FASEB J, 31, 2973-2980 (2017)
21. Shimura M, Shindou H, Szyrwiel L, Tokuoka SM, Hamano F, Matsuyama S, Okamoto M, Matsunaga A, Kita Y, Ishizaka Y., Yamauchi K, Kohmura Y, Lobinski R, Shimizu I, Shimizu T. Imaging of intra-cellular fatty acids by scanning X-ray fluorescence microscopy. FASEB J. 30, 4149-4158 (2016) Epub.
22. Kita Y, Yoshida K, Tokuoka MS, Hamano F, Yamazaki M, Sakimura K, Kano M, Shimizu T. Fever is mediated by conversion of endocannabi-

noid 2-arachidonoylglycerol to prostaglandin E2. PLoS ONE, 10, e0133663 (2015)
23. Harayama T, Shindou H, Kita Y, Otsubo E, Ikeda K, Chiba S, Weaver T, Shimizu T. Establishment of LC-MS method for the analysis of palmitoylated surfactant proteins. J. Lipid Res., 56, 1370-1379 (2015)
24. Yamada M, Kita Y, Kohira T, Yoshida K, Hamano F, Tokuoka SM, Shimizu T. A comprehensive quantification method for eicosanoids and related compounds by using liquid chromatography/mass spectrometry with high speed continuous ionization polarity switching. J. Chrom. B, 995, 74-84 (2015)

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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, 2020, which is a social collaboration department with NIPPON TELEGRAPH AND TELEPHONE CORPORATION (NTT), Suntory Wellness Ltd., 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 have completed the baseline study in 2005-2007, then, 2nd, 3rd, 4th, and 5th follow-ups were completed in 2008-2010, 2012-2013, 2015-2016, and 2018-2019 respectively. We have been conducting further follow-up surveys.

References

1. Suzuki T, Nishita Y, Jeong S, Shimada H, Otsuka R, Kondo K, Kim H, Fujiwara Y, Awata S, Kitamura A, Obuchi S, Iijima K, Yoshimura N, Watanabe S, Yamada M, Toba K, Makizako H: Are Japanese older adults rejuvenating? Changes in health-related measures among older community dwellers in the last decade. Rejuvenation Research 24(1), 37-46, 2021
2. Leyland KM, Gates LS, Nevitt M, Felson D, Jones G, Jordan JM, Judge A, Sanchez-Santos MT, Sheard S, Yoshimura N, Newton J, Cooper C, Lin J, Liu Q, Collins G, Altman D, Arden NK, and the PCCOA steering committee: Knee osteoarthritis and time-to all-cause mortality in six community-based cohorts: an international analysis of individual participant-level data. Aging Clin Exp Res 33(3), 529-545, 2021.
3. Makizako H, Nishita Y, Seungwon J, Otsuka R,

Shimada H, Iijima K, Obuchi S, Kim H, Kitamura A, Ohara Y, Awata S, Yoshimura N, Yamada M, Toba K, Suzuki T: Trends in the prevalence of frailty in Japan: A meta-analysis from the ILSA-J. The Journal of Frailty & Aging 10(3): 211-218, 2021.

4. Taniguchi T, Harada T, Iidaka T, Hashizume H, Taniguchi W, Oka H, Asai Y, Muraki S, Akune T, Nakamura K, Kawaguchi H, Yoshida M, Tanaka S, Yamada H, Yoshimura N: Prevalence and associated factors of pistol grip deformity in a Japanese population: The ROAD Study. Scic Rep 11(1), 6025, 2021.
5. Miyamoto K, Hirayama A, SatoY, Ikeda S, Maruyama M, Soga T, Tomita M, Yoshimura N, Miyamoto T: Metabolomic profile predictive of new osteoporosis or sarcopenia development. Metabolites 11(5), 278, 2021.
6. Otsuka Y, Iidaka T, Horii C, Muraki S, Oka H, Nakamura K, Izumo T, Rogi T, Shibata H, Tanaka S, Yoshimura N: Dietary intake of vitamin E and fats associated with sarcopenia in community-dwelling older Japanese people: A cross-sectional study from the fifth survey of the ROAD study. Nutrients 13(5), 1730, 2021.
7. Hira K, Nagata K, Hashizume H, Asai Y, Oka H, Tsutsui S, Takami M, Iwasaki H, Muraki S, Akune T, Iidaka T, Kawaguchi H, Nakamura K, Yoshida M, Tanaka S, Yoshimura N, Yamada H: Relationship of sagittal spinal alignment with low back pain and physical performance in the general population. Sci Rep 11(1): 20604, 2021.
8. Mera Y, Teraguchi M, Hashizume H, Oka H, Muraki S, Akune T, Kawaguchi H, Nakamura K, Tamai H, Tanaka S, Yoshida M, Yoshimura N, Yamada H: Association between types of Modic changes in the lumbar region and low back pain in a large cohort: the Wakayama spine study. Eur Spine J 30(4): 1011-1017, 2021.
9. Teraguchi M, Hashizume H, Oka H, Cheung JPY, Samartzis D, Tamai H, Muraki S, Akune T, Tanaka S, Yoshida M, Yoshimura N, Yamada H: Detailed subphenotyping of lumbar modic changes and their association with low back pain in a large population-based study: The Wakayama Spine Study. Pain Ther 11(1):57-71, 2022.
10. Horii C, Iidaka T, Muraki S, Oka H, Asai Y, Tsutsui S, Hashizume H, Yamada H, Yoshida M, Kawaguchi H, Nakamura K, Akune T, Oshima Y, Tanaka S, Yoshimura N: The cumulative incidence and risk factors for morphometric severe vertebral fractures in Japanese men and women: the ROAD study third and fourth surveys. Osteoporos Int 33:889-899, 2022.
11. Shoji A, Gao Z, Arai K, Yoshimura N: Trends in incidence of osteoporosis-related fractures in Japan over the past 30 years: A systematic review and meta-analysis. J Bone Miner Metab 40(2):327-336, 2022.
12. Asai Y, Tsutsui S, Yoshimura N, Hashizume H, Iidaka T, Horii C, Kawaguchi H, Nakamura K, Tanaka S, Yoshida M, Yamada H.: Relationship between age-related spinopelvic sagittal alignment and low back pain in adults of population-based cohorts: The ROAD Study. J Pain Research 15:33-38, 2022.
13. Matsumoto T, Higuchi J, Maenohara Y, Chang Song Ho, Iidaka T, Horii C, Oka H, Muraki S, Hashizume H, Yamada H, Yoshida M, Nakamura K, Tanaka S, Yoshimura N: The discrepancy between radiographically-assessed and self-recognized hallux valgus in a large population-based cohort. BMC Musculoskeletal Disorders 23(1):31, 2022.

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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 2021, 219,932 outpatient blood sampling were performed in this section. Furthermore, 256,874 urine samples were examined.

The 2nd Section

This section deals with clinical biochemistry and immuno-serology tests. In 2021, 5,447,680 serum enzyme tests (such as AST and ALT), and 572,737 immunological tests were performed.

The 3rd Section

This section deals with laboratory hematology and diabetes-related tests, and gene analysis tests. In 2021, 1,164,555 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 2021, 42,787 ECG, 18,193 pulmonary function tests, and 10,738 EEG were performed.

The 5th Section

This section deals with ultrasonography. In 2021, 12,073 echocardiography tests, 13,816 abdominal echography tests, and 12,170 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) development of COVID-19-associated biomarkers, iv) platelet biology, development of laboratory diagnosis in thrombosis and hemostasis, v) cancer genomic medicine using next generation sequencing, vi) oxidized albumin as a redox marker, vii) echocardiographic studies of the pathophysiology of valvular heart disease and the hemodynamics, viii) neuroscience research using magnetoencephalography and non-invasive brain stimulation, and ix) promotion of medical-science-engineering cooperation.

References

Original article:

1. Chou, S., Yasukawa, K., Fujino, Y., Ishibashi, M., Haraguchi, M., Sato, M., Ikeda, H., Nakamura, S., and Yatomi, Y. Non-mercaptalbumin is significantly associated with the coronary plaque burden and the severity of coronary artery disease. ***Sci. Rep***.11: 14242, 2021.
2. Hirose, K., Nakanishi, K., Daimon, M., Sawada, N., Yoshida, Y., Iwama, K., Yamamoto, Y., Ishiwata, J., Hirokawa, M., Koyama, K., Morita, H., Di, Tullio, M.R., Homma, S., and Komuro I. Impact of insulin resistance on subclinical left ventricular dysfunction in normal weight and overweight/obese japanese subjects in a general community. ***Cardiovasc. Diabetol***. 20: 22, 2021.
3. Honjo, M., Yamagishi, R., Igarashi, N., Ku, C.Y., Kurano, M., Yatomi, Y., Igarashi, K., and Aihara, M. Effect of postoperative corticosteroids on surgical outcome and aqueous autotaxin following combined cataract and microhook ab interno trabeculotomy. ***Sci. Rep***. 11: 747, 2021.
4. Igarashi, N., Honjo, M., Asaoka, R., Kurano, M., Yatomi, Y., Igarashi, K., Miyata, K., Kaburaki, T., and Aihara, M. Aqueous autotaxin and TGF-βs are promising diagnostic biomarkers for distinguishing open-angle glaucoma subtypes. ***Sci. Rep***. 11: 1408, 2021.
5. Igarashi, N., Honjo, M., Yamagishi, R., Kurano, M., Yatomi, Y., Igarashi, K., Kaburaki, T., and Aihara, M. Crosstalk between transforming growth factor beta-2 and Autotaxin in trabecular meshwork and different subtypes of glaucoma. ***J. Biomed. Sci.***28: 47, 2021.
6. Isago, H., Mitani, A., Kohno, S., Nagoshi, S., Ishimori, T., Saito, M., Tamiya, H., Miyashita, N., Ishii, T., Matsuzaki, H., Yatomi, Y., Nagase, T., and Jo, T. The Japanese Herbal (Kampo) Medicine Hochuekkito Attenuates Lung Inflammation in Lung Emphysema. ***Biol. Pharm. Bull.*** 44: 39-45, 2021.
7. Ishihara, Y., Okamoto, K., Shimosaka, H., Ono, Y., Kanno, Y., Ikeda, M., Harada, S., Kurano, M., Okugawa, S., Moriya, K., and Yatomi Y. Prevalence and clinical characteristics of patients with biologically false-positive reactions with

serological syphilis testing in contemporary practice: 10-year experience at a tertiary academic hospital. ***Sex. Transm. Infect.*** 97: 397-401, 2021.

8. Iwata, Y., Kitajima, S., Yamahana, J., Shimomura, S., Yoneda-Nakagawa, S., Sakai, N., Furuichi, K., Ogura, H., Sato, K., Toyama, T., Yamamura, Y., Miyagawa, T., Hara, A., Shimizu, M., Ohkawa, R., Kurano, M., Yatomi, Y., and Wada, T. Higher serum levels of autotaxin and phosphatidylserine-specific phospholipase A1 in patients with lupus nephritis. ***Int. J. Rheum. Dis***. 24: 231-239, 2021.
9. Kaneko, H., Kiriyama, H., Kamon, T., Itoh, H., Kodera, K., Fujiu, K., Daimon, M., Morita, H., Hatano, M., and Komuro, I. Percutaneous mitral valve intervention using MitraClip for functional mitral regurgitation and heart failure. I***nt. Heart J.*** 62: 4-8, 2021.
10. Kano, K., Matsumoto, H., Kono, N., Kurano, M., Yatomi, Y., and Aoki, J. Suppressing postcollection lysophosphatidic acid metabolism improves the precision of plasma LPA quantification. ***J. Lipid Res.*** 62: 100029, 2021.
11. Kamon, T., Kaneko, H., Kiriyama, H., Itoh, H., Fujiu, K., Kumazawa, R., Morita, K., Michihata, N., Jo, T., Miura, M., Kodera, S., Uehara, M., Ando, J., Inoue, T., Kinoshita, O., Yamauchi, H., Mori, Y., Nakao, T., Daimon, M., Takeda, N., Morita, H., Ono, M., Yasunaga, H., and Komuro, I. Transcatheter aortic valve implantation and surgical aortic valve replacement for aortic stenosis in Japan; Analysis of a nationwide inpatient database. ***Circ. Rep***. 2: 753–758, 2021.
12. Kiriyama, H., Kaneko, H., Itoh, H., Kamon, T., Morita, K., Jo, T., Fujiu, K., Daimon, M., Takeda, N., Morita, H., Yasunaga, H., and Komuro I. Surgical treatment for infective endocarditis in the ageing society: a nationwide retrospective study in Japan. ***Open Heart*** 8: e001627, 2021.
13. Kobayashi, T., Kurano, M., Nanya, M., Shimizu, T., Ohkawa, R., Tozuka, M., and Yatomi, Y. Glycation of HDL Polymerizes Apolipoprotein M and Attenuates Its Capacity to Bind to Sphingosine 1-Phosphate. ***J. Atheroscler. Thromb.*** 28: 730-741, 2021.
14. Kurano, M., Kobayashi, T., Sakai, E., Tsukamoto, K., and Yatomi, Y. Lysophosphatidylinositol, especially albumin-bound form, induces inflammatory cytokines in macrophages. ***FASEB J.*** 35: e21673, 2021.
15. Mitani, A., Hamada, K., Yoshikawa, N., Morita, Y., Horie, T., Inoue, Y., Saito, M., Ishii, T., Sunohara, M., Takahashi, R., Emoto, N., Nishimoto, N., Murano, Y., Okazaki, S., Tateishi, S., Yao, A., Shimura, T., Kurano, M., Yatomi, Y., and Yanagimoto, S. Epidemiological study using IgM and IgG antibody titers against SARS-CoV-2 in The University of Tokyo, Japan (UT-CATS). ***J. Infect. Chemother***. 27: 1342-1349, 2021.
16. Morita, Y., Kurano, M., Sakai, E., Sawabe, M., Aoki, J., Yatomi, Y. Simultaneous analyses of urinary eicosanoids and related mediators identified tetranor-prostaglandin E metabolite as a novel biomarker of diabetic nephropathy. ***J. Lipid Res***. 62: 100120, 2021.
17. Nakamura, N., Honjo, M., Yamagishi, R., Kurano, M., Yatomi, Y., Watanabe, S., and Aihara, M. Neuroprotective role of sphingolipid rheostat in excitotoxic retinal ganglion cell death. ***Exp. Eye. Res.***208: 108623, 2021.
18. Nakano, Y., Kurano, M., Morita, Y., Shimura, T., Yokoyama, R., Qian, C., Xia, F., He, F., Kishi, Y., Okada, J., Yoshikawa, N., Nagura, Y., Okazaki, H., Moriya, K., Seto, Y., Kodama, T., and Yatomi Y. Time course of the sensitivity and specificity of anti-SARS-CoV-2 IgM and IgG antibodies for symptomatic COVID-19 in Japan. ***Sci. Rep.*** 11: 2776, 2021.
19. Nakanishi, K., Daimon, M., Yoshida, Y., Ishiwata, J., Sawada, N., Hirose, K., Iwama, K., Yamamoto, Y., Hirokawa, M., Kaneko, H., Nakao, T., Mizuno, Y., Morita, H., Di, Tullio, M.R., Yatomi, Y., Homma, S., and Komuro I. Relation of Body Mass Index to Adverse Right Ventricular Mechanics. ***Am. J. Cardiol.*** 144: 137-142, 2021.
20. Nishikawa, M., Kanno, H., Zhou, Y., Xiao, TH., Suzuki, T., Ibayashi, Y., Harmon, J., Takizawa, S., Hiramatsu, K., Nitta, N., Kameyama, R., Peterson, W., Takiguchi, J., Shifat-E-Rabbi, M., Zhuang, Y., Yin, X., Rubaiyat, AHM., Deng, Y., Zhang, H., Miyata, S., Rohde, GK., Iwasaki, W., Yatomi, Y., and Goda, K. Massive image-based single-cell profiling reveals high levels of circulating platelet aggregates in patients with COVID-19. ***Nat Commun.*** 12: 7135, 2021.

21. Osawa, I., Okamoto, K., Ikeda, M., Otani, A., Wakimoto, Y., Yamashita, M., Shinohara, T., Kanno, Y., Jubishi, D., Kurano, M., Harada, S., Okugawa, S., Yatomi, Y., and Moriya, K. Dynamic changes in fibrinogen and D-dimer levels in COVID-19 patients on nafamostat mesylate. ***J. Thromb. Thrombolysis***. 51: 649-656, 2021.
22. Sato, M., Tateishi, R., Yatomi, Y., and Koike, K. Artificial intelligence in the diagnosis and management of hepatocellular carcinoma. ***J. Gastroenterol. Hepatol.*** 36: 551-560, 2021.
23. Shimura, T., Kurano, M., Kanno, Y., Ikeda, M., Okamoto, K., Jubishi, D., Harada, S., Okugawa, S., Moriya, K., and Yatomi, Y. Clot waveform of APTT has abnormal patterns in subjects with COVID-19. ***Sci. Rep.*** 11: 5190, 2021.
24. Soulat-Dufour, L., Addetia, K., Miyoshi, T., Citro, R., Daimon, M., Gutierrez, Fajardo, P., Kasliwal, R.R., Kirkpatrick, J.N., Monaghan, M.J., Muraru, D., Ogunyankin, K.O., Park, S.W., Ronderos, R.E., Sadeghpour, A., Scalia, G.M., Takeuchi, M., Tsang, W., Tucay, E.S., Tude, Rodrigues, A.C., Vivekanandan, A., Zhang, Y., Diehl, M., Schreckenberg, M., Mor-Avi, V., Asch, F.M., and Lang, R.L. Normal values of right atrial size and function according to age, sex and ethnicities: Results of the World Alliance of Societies of Echocardiography study. ***J. Am. Soc. Echocardiogr.*** 34: 286-300, 2021.
25. Sugawara, M., Hoshina, K., Chigira, M., Suzuki, H., Daimon, M., Takayama, T., Ono, Y., and 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 Medical Case Reports*** 9: 1-3, 2021.
26. Sugawara, M., Nakao, T., Yatomi, Y., and Daimon, M. Development of aortic regurgitation due to non-bacterial thrombotic endocarditis. ***J. Med. Ultrason (2001)***. 48: 363–364, 2021.
27. Takami, A., Watanabe, S., Yamamoto, Y., Kondo, H., Bamba, Y., Ohata, M., Mishima, S., Kubota, H., Nishiura, A., Miura, R., Iwagami, M., Higashi, K., Yatomi, Y., Tohyama, K., Japanese Society for Laboratory Hematology Standardization, C., Joint Working Group of the, J., and the Japanese Association of Medical, T. Reference intervals of red blood cell parameters and platelet count for healthy adults in Japan. Int. ***J. Hematol.*** 114: 373-380, 2021.
28. Tanaka, R., Kaburaki, T., Taoka, K., Karakawa, A., Tsuji, H., Nishikawa, M., Yatomi, Y., Shinozaki-Ushiku, A., Ushiku, T., and Araki, F. More Accurate Diagnosis of Vitreoretinal Lymphoma Using a Combination of Diagnostic Test Results: A Prospective Observational Study. ***Ocul. Immunol. Inflamm***. 4: 1-7, 2021.
29. Takano, H., Yasunaga, M., Yamazaki, I., Nishikawa, M., Masamoto, Y., Shinozaki-Ushiku, A., Kawakami, M., Yatomi, Y., and Kurokawa, M. Degenerated mitochondria in leukemic blast appeared as granules on May-Grunwald-Giemsa staining. ***Ann Hematol***. 10, 2021. Online ahead of print.
30. Tarao, K., Daimon, M., Son, K., Nakanishi, K., Nakao, T., Suwazono, Y., Isono, S. Risk factors including preoperative echocardiographic parameters for post-induction hypotension in general anesthesia. ***J. Cardiol.*** 78: 230-236, 2021.
31. Tokuoka, S.M., Kita, Y., Sato, M., Shimizu, T., Yatomi, Y., and Oda, Y. Development of Tandem Mass Tag Labeling Method for Lipid Molecules Containing Carboxy and Phosphate Groups, and Their Stability in Human Serum. ***Metabolites.*** 11: 19, 2021.
32. Tsuchida, R., Tanabe, Y., Nishizawa, D., Ikeda, K., Abe, H., Inoue, R., Kurano, M., Yatomi, Y., Tamura, K., Takano, T., Shimizu, C., Uchida, K., and Sumitani, M. Genetic polymorphisms of lysophosphatidic acid receptor 1 are associated with the onset of taxane-induced peripheral neuropathy. ***Br. J. Anaesth.*** 7: e43-e46 ,2021.
33. Uranbileg, B., Ito, N., Kurano, M., Kano, K., Uchida, K., Sumitani, M., Aoki, J., and Yatomi Y. Inhibition of autotaxin activity ameliorates neuropathic pain derived from lumbar spinal canal stenosis. ***Sci. Rep***. 11: 3984, 2021.
34. Xu, B., Daimon, M., Kawata, T., Nakao, T., Hirokawa, M., Sawada, N., Kimura, K., Yamanaka, Y., Morita, H., Komuro, I., and Yatomi Y. Relationship Between Mitral Leaflet Size and Coaptation and Their Associated Factors in Patients with Normal Left Ventricular Size and Systolic Function. ***Int. Heart J.*** 62: 95-103, 2021.

35. Xu, B., Kawata, T., Nakao, T., Nakanishi, K., Hirokawa, M., Sawada, N., Kimura, K., Abe, Y., Komuro, I., Yatomi, Y., and Daimon, M. Mitral Valvular Coaptation-Zone Area Is Associated with the Severity of Atherosclerosis Assessed by Cardio-Ankle Vascular Index. ***Int. Heart J***.62: 552-558, 2021.
36. Yasuda, N., Nishikawa, M., Shimosaka, H., Ono, Y., and Yatomi, Y. Effect of administration of immunoglobulin preparations on the results of tests for autoantibodies. ***Mod. Rheumatol.*** roab085, 2021.
37. Yokoyama, R., Kurano, M., Morita, Y., Shimura, T., Nakano, Y., Qian, C., Xia, F., He, F., Kishi, Y., Okada, J., Yoshikawa, N., Nagura, Y., Okazaki, H., Moriya, K., Seto, Y., Kodama, T., and Yatomi, Y. Validation of a new automated chemiluminescent anti-SARS-CoV-2 IgM and IgG antibody assay system detecting both N and S proteins in Japan. ***PLoS One.*** 16: e0247711, 2021.
38. Yokoyama, R., Kurano, M., Nakano, Y., Morita, Y., Ohmiya, H., Kishi, Y., Okada, J., Qian, C., Xia, F., He, F., Zheng, L., Yu, Y., Jubishi, D., Okamoto, K., Moriya, K., Kodama, T., and Yatomi, Y. Association of the serum levels of the nucleocapsid antigen of SARS-CoV-2 with the diagnosis, disease severity, and antibody titers in patients with COVID-19: a retrospective cross-sectional study. ***Front. Microbiol.*** 12: 791489, 2021.
39. Yoshida, Y., Nakanishi, K., Daimon, M., Ishiwata, J., Sawada, N., Hirokawa, M., Kaneko, H., Nakao, T., Mizuno, Y., Morita, H., Di, Tullio, M.R., Homma, S., and Komuro, I. Sex-specific Difference in the Association Between Arterial Stiffness and Subclinical Left Ventricular Dysfunction. ***Eur. Heart. J.*** Cardiovasc. Imaging 22: 817-823, 2021.

Surgical Center

Professor (Director)

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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, 9921, 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) and 11,047 operations were performed in 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018, 2019, 2020 and 2021 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, de-contamination/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.

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
12) Maintenance and management of surgical equipment
13) Nutritional management of perioperative patients
14) Others

Radiology Center

Professor (Director)
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Lecturer (Vice Director)
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Chief Technologist (Vice Director)
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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, 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), Wataru Gonoi (Vice Director/Lecturer), Masaki Katsura (Project Lecturer), 77 radiology technologists, including Chief Technologist Hideyuki Iwanaga, 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 started its practical operation in 2015. 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.

2) Nuclear Medicine Section:

The nuclear medicine section is responsible for various nuclear medicine examinations (gamma camera, single-photon emission computerized tomography (SPECT), positron emission tomography (PET)), radiopharmaceutical management, production of PET nuclides using accelerators, label synthesis, quality verification, radioactive contaminant management, internal isotope irradiation 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, renal, 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 18F-fluorodeoxyglucose-PET (FDG-PET) in cases of malignant tumors. PET examinations using tracers labeled with positron nuclides (18F) 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 2009, we started internal radioisotope therapy for castration-resistant prostate cancer with bone metastasis and radioimmunotherapy for malignant lymphoma.

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 Inpatient Ward 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 2014, one of the linear accelerators was upgraded, and a tomotherapy was introduced. Tomotherapy is a helical intensity-modulated machine dedicated to high-precision radiotherapy for brain and head and neck tumors, whole-body irradiation, and whole-body skin irradiation. The Radiology Information System (RIS), introduced in 2012 from the viewpoint of medical safety, is now in operation to construct a comprehensive management system for cancer treatment. Recently, the gamma-knife system was updated in February 2019, and image-guided radiotherapy is now available in the gamma-knife system.

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 Medical Service Law and the Law Concerning Prevention of Radiation Hazards Act on the Prevention of Hazards to Persons with Disabilities.

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 Ward 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 2021.4 to 2022.3

	Inpatient	Outpatient	Total
Radiography (plain)	85,938	70,930	156,868
Radiography (enhanced)	3,849	1,390	5,239
Angiography	3,436	17	3,453
Computed tomography	13,798	36,933	50,731
Magnetic resonance imaging	4,692	16,314	21,006
Nuclear medicine	1,471	3,003	4,474
Radiotherapy	4,659	8,427	13,086
Bone mineral densitometry	287	2,556	2,843

Department of Pharmacy

Professor

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Lecturer

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Introduction and Organization

We have 8 faculty members, 83 pharmacy staffs, and 8 graduate students and 8 undergraduate students from the faculty of pharmaceutical sciences (as of March 1st, 2022).

Clinical activities

Department of Pharmacy consists of the following six sections:

1) Drug information and research 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). In order to support advanced medical care, they develop and check formulations (characterization of the uniformity, stability and so on) of the medicine which 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 (2,681 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 2021)
Number of items on in-hospital formulary: 2,681
Number of prescriptions (ps.) filled or preparation (pp.) (annual)

out-patients	:	331,929 ps.
(outside	:	301,517 ps.)
(inside	:	30,412 ps.)
out-patient chemotherapy	:	12,539 ps.
in-patients	:	236,172 ps.
injection drugs	:	185,108 ps.
IVH	:	2,949 pp.
chemotherapy	:	11,565 pp.
TDM consultations (annual)	:	20,788 pp.

Numbers of hospital pharmaceutical cares (annual): 23,311 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 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 2021, 9 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. Elucidation of the molecular mechanism which controls *in vivo* disposition of lipids / bile acids / uric acid, and establishment of new therapy for life-style related diseases based on those integrated understanding.
2. Elucidation of the dynamic regulatory mechanism of bone resorption / bone formation, and establishment of new therapy for bone metabolic disease based on those integrated understanding.
3. Establishment of the way to quantitative understanding and prediction of pharmacological-effect and adverse-effect of drugs directed against particular molecular target. Finally, these outputs would be feedbacked to early drug development stages.
4. Elucidation of the molecular mechanism related to the adverse effect of drugs using large-scale "-omics" analysis. Finally, the quantitative information would be applied to develop strategies to prevent / treat the adverse effect.
5. Absolute quantification of factors determining the pharmacokinetic profiles of drugs and its application to clinical pharmacokinetics and pharmacology field.

Publications

(1) Kawamura Y, Nakayama A, Shimizu S, Toyoda Y, Nishida Y, Hishida A, Katsuura-Kamano S, Shibuya K, Tamura T, Kawaguchi M, Suzuki S, Iwasawa S, Nakashima H, Ibusuki R, Uemura H, Hara M, Takeuchi K, Takada T, Tsunoda M, Arisawa K, Takezaki T, Tanaka K, Ichida K, Wakai K, Shinomiya N, Matsuo H. A proposal for practical diagnosis of renal hypouricemia: Evidenced from genetic studies of nonfunctional variants of URAT1/SLC22A12 among 30,685 Japanese individuals. ***Biomedicines.*** 2021;9:1012.

(2) Mitsuboshi S, Yamaguchi R, Uchida H, Kamoshida S, Hashi H. Inappropriate use of ozone generators and their sales status: Questionnaire survey of healthcare providers and investigation of online sales. ***J Hosp Infect.*** 2021;117:1-3.

(3) Nara K, Taguchi A, Tojima Y, Miyamoto Y, Tanikawa M, Sone K, Mori M, Tsuruga T, Yamamoto T, Takenaka R, Takada T, Osuga Y, Suzuki H. History of whole pelvis plus para-aortic radiation is a risk factor associated with febrile neutropenia during chemotherapy for recurrent cervical cancer. ***Int J Clin Oncol.*** 2021;26:1759-66.

(4) Ogura M, Toyoda Y, Sakiyama M, Kawamura Y, Nakayama A, Yamanashi Y, Takada T, Shimizu S, Higashino T, Nakajima M, Naito M, Hishida A, Kawai S, Okada R, Sasaki M, Ayaori M, Suzuki H,

Takata K, Ikewaki K, Harada-Shiba M, Shinomiya N, Matsuo H. Increase of serum uric acid levels associated with apoE ε2 haplotype: A clinico-genetic investigation and *in vivo* approach. ***Hum Cell.*** 2021;34:1727-33.

(5) Takaoka R, Soejima Y, Guro S, Yoshioka H, Sato H, Suzuki H, Hisaka A. Model-based meta-analysis of changes in circulatory system physiology in patients with chronic heart failure. ***CPT Pharmacometrics Syst Pharmacol.*** 2021;10:1081-91.

(6) Taniguchi T, Omura K, Motoki K, Sakai M, Chikamatsu N, Ashizawa N, Takada T, Iwanaga T. Hypouricemic agents reduce indoxyl sulfate excretion by inhibiting the renal transporters OAT1/3 and ABCG2. ***Sci Rep.*** 2021;11:7232.

(7) Toyoda Y, Kawamura Y, Nakayama A, Nakaoka H, Higashino T, Shimizu S, Ooyama H, Morimoto K, Uchida N, Shigesawa R, Takeuchi K, Inoue I, Ichida K, Suzuki H, Shinomiya N, Takada T, Matsuo H. Substantial anti-gout effect conferred by common and rare dysfunctional variants of URAT1/SLC22A12. ***Rheumatology (Oxford).*** 2021;60:5224-32.

(8) Toyoda Y, Pavelcova K, Bohata J, Jesina P, Kubota Y, Suzuki H, Takada T, Stiburkova B. Identification of two dysfunctional variants in the ABCG2 urate transporter associated with pediatric-onset of familial hyperuricemia and early-onset gout. ***Int J Mol Sci.*** 2021;22:1935.

Rehabilitation Center

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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 moxbustion. 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

Central Supply Service

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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

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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. We also started Outpatient Clinic of Pathology to provide detailed information and explanation about pathologic diagnosis to the patients with breast cancer.

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 Geneprofiling of

malignant solid tumors' was conducted which enrolled 200 patients. In addition, cancer panel testing covered by public health insurance (NCC Oncopanel and FoundationOne CDx) started in November 2019. We serve as members of expert panel to contribute to the promotion of genomic medicine.

Clinical activities (diagnostic pathology and autopsy)

The annual statistics of the pathology practice in 2021 fiscal year consisted of 17,434 surgical cases, 15,098 cytology, 824 intraoperative histologic diagnosis, 372 intraoperative cytology, 33 autopsy cases (autopsy rate, 10.4%). The numbers of surgical and cytology cases returned to those before COVID-19 pandemic, while the numbers of intraoperative diagnosis and autopsy cases remained small due to 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. Yamauchi,Tanaka and Rokutan), liver metastasis (Dr. Abe), and female genital tracts (Drs. Ikemura and Iwasaki), 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 multiplex genomic testing. We also join clinico-pathologic and genomic conference which is held every week to present histology of the cases and join the discussion. Conventional companion diagnoses using immunohistochemistry and FISH are also provided.

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 seven junior residents (total 16 months) in 2021 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 useful-ness 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

(Only case reports are provided here. Original articles are included in the section of "Department Pathology and Diagnostic Pathology")

1. Ando T, Kage H, Shinozaki-Ushiku A, Tatsuno K, Tsutsumi S, Nagayama K, Nakajima J, Kohsaka S, Miyagawa K, Aburatani H, Mano H, Nagase T. Composite Clonal Analysis Reveals Transition of NSCLC Subtypes Through Accumulation of Gene Mutations: A Case Report. JTO Clin Res Rep. 2022;3(2):100277.
2. Ideyama M, Abe H, Mori K, Yamagata Y, Seto Y, Ushiku T. Acquired mini-stomach development in the esophagus after caustic injury. Pathol Int. 2021;71(11):792-794.
3. Ishigami D, Miyawaki S, Nakatomi H, Takayanagi S, Teranishi Y, Ohara K, Hongo H, Dofuku S, Kin T, Abe H, Mitsui J, Komura D, Katoh H, Ishikawa S, Saito N. Brainstem intraparenchymal schwannoma with genetic analysis: a case report and literature review. BMC Med Genomics. 2021;14(1):205.
4. Kaneko M, Nozawa H, Rokutan H, Murono K, Ushiku T, Ishihara S. Ectopic decidua of the appendix: a case report. Surg Case Rep. 2021; 7(1):117.
5. Kato S, Kubota Y, Sekiguchi M, Watanabe K, Shinozaki-Ushiku A, Takita J, Hiwatari M. KMT2A-rearranged diffuse large B-cell lymphoma in a child: a case report and molecular characterization. Pediatr Hematol Oncol. 2021; 38(3):281-289.
6. Kobayashi H, Makise N, Shinozaki-Ushiku A, Ishibashi Y, Ikegami M, Kohsaka S, Ushiku T, Oda K, Miyagawa K, Aburatani H, Mano H, Tanaka S. Scapular Angiomatoid Fibrous Histiocytoma with EWSR1-CREB1 Fusion in an Adult Patient. Case Rep Orthop. 2021;2021: 9434222.
7. Makise N, Yoshida KI, Iijima T, Yoshida A, Ushiku T, Ishida T. Skeletal EWSR1-NFATC2 sarcoma previously diagnosed as Ewing-like adamantinoma: A case report and literature review emphasizing its unique radiological features. Pathol Int. 2021;71(9):614-620.
8. Murakami D, Maki H, Matsuda K, Masamoto Y, Suzuki F, Amemiya S, Osawa K, Hinata M, Ikemura M, Ushiku T, Kurokawa M. Cerebral toxoplasmosis complicating lymphoplasmacytic lymphoma in partial remission. J Infect Chemother. 2022;28(2):279-282.
9. Nakazaki K, Yoshida M, Masamoto Y, Shinozaki-Ushiku A, Ikemura M, Hisamoto T, Yasunaga M, Sato S, Kurokawa M. Discordant lymphomas of classic Hodgkin lymphoma and peripheral T-cell lymphoma following dupilumab treatment for atopic dermatitis. Int J Hematol. 2022;Epub ahead of print.
10. Ohki D, Tsuji Y, Yamazawa S, Ushiku T, Tateishi K. Gastrointestinal: Esophageal adenocarcinoma arising from circumferential ectopic gastric mucosa: A case report. J Gastroenterol Hepatol. 2022;37(1):47.
11. Sakamoto A, Nozawa H, Sonoda H, Hinata M, Ishii H, Emoto S, Anzai H, Yokoyama Y, Murono K, Sasaki K, Kawai K, Ushiku T, Ishihara S. Rectal neuroendocrine tumor with extracapsular lymph node metastasis: a case report. Clin J Gastroenterol. 2021;14(5):1426-1430.
12. Sasaki K, Honda A, Shinozaki-Ushiku A, Fujioka Y, Maki H, Toyama K, Ushiku T, Kurokawa M. A case of transplantation-associated thrombotic microangiopathy with autopsy-proven fatal myocardial ischemia after allogeneic hematopoietic stem cell transplantation. Ann Hematol. 2021;100(6):1621-1622.
13. Sone K, Inoue F, Taguchi A, Hinata M, Ikemura M, Miyamoto Y, Michihiro T, Ohno T, Iriyama T, Mori-Uchino M, Tsuruga T, Mishima M, Osuga Y. A case of difficult-to-diagnose non-invasive papillary squamous cell carcinoma of the uterine cervix infected with human papilloma virus 6: A diagnostic pitfall. Clin Case Rep. 2021;9(10): e04905.
14. Sone K, Kukita A, Masui Y, Yamada D, Shinozaki-Ushiku A, Kawata A, Taguchi A, Miyamoto Y, Tanikawa M, Iriyama T, Mori-Uchino M, Tsuruga T, Osuga Y. Recurrent malignant melanoma of the uterine cervix treated with anti-PD-1 antibodies and anti-CTLA-4

antibodies: A case report. Mol Clin Oncol. 2022; 16(3):63.
15. Suzuki S, Kurokawa R, Tsuruga T, Mori-Uchino M, Nishida H, Kato T, Abe H, Ushiku T, Amemiya S, Katayama A, Abe O. CT, MRI, and FDG-PET imaging findings of low-grade extrauterine endometrial stromal sarcoma arising from the mesentery:A case report. Radiol Case Rep. 2021;16(9):2774-2779.
16. Tachikawa Y, Nozawa H, Hata K, Abe H, Ushiku T, Ishihara S. Metachronous ileal cancer after surgery for ascending colon cancer in a patient with Lynch syndrome: A case report. Int J Surg Case Rep. 2021;81:105714.
17. Taguchi A, Rokutan H, Oda K, Tanikawa M, Tanimoto S, Sone K, Mori M, Tsuruga T, Kohsaka S, Tatsuno K, Shinozaki-Ushiku A, Miyagawa K, Mano H, Aburatani H, Ushiku T, Osuga Y. Genetic diagnosis of pseudomyxoma peritonei originating from mucinous borderline tumor inside an ovarian teratoma. BMC Med Genomics. 2022;15(1):51.
18. Takamiya A, Ishibashi Y, Makise N, Hirata M, Ushiku T, Tanaka S, Kobayashi H. Imaging characteristics of NTRK-rearranged spindle cell neoplasm of the soft tissue: A case report. J Orthop Sci. 2022;S0949-2658(21)00367-5.
19. Tsuda Y, Kobayashi H, Makise N, Zhang L, Shinoda Y, Ushiku T, Tanaka S. Hemangioma of the Rib Mimicking Chondrosarcoma: A Report of Two Cases and Literature Review. Case Rep Orthop. 2021;2021:9996380.
20. Tsuzuki S, Komai T, Terada K, Tsuchida Y, Tanaka M, Tateishi Y, Shinozaki-Ushiku A, Shoda H, Fujio K. Nailfold capillaroscopic abnormalities in angioedema with eosinophilia. Allergol Int. 2021;70(4):501-503.
21. Yamamoto A, Tateishi Y, Aikou S, Seto Y, Ushiku T. The first case of gastric leiomyosarcoma developed through malignant transformation of leiomyoma. Pathol Int. 2021; 71(12):837-843.

Department of Corneal Transplantation

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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 keratopasty, 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: PMC 8666511.

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

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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 1100 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 2021, 17 patients (including 1 children) received autologous HSCT and 29 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 preconditioning 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.

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.

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. Sasaki K, Honda A, Shinozaki-Ushiku A, Fujioka Y, Maki H, Toyama K, UshikuT, and Kurokawa M. A case of transplantation-associated thrombotic microangiopathy with autopsy-proven fatal myocardial ischemia after allogeneic hematopoietic stem cell transplantation. Annals of Hematology, 100(6): 1621-1622,2021.
2. Yasunaga M, Yasuda Y, Honda A, Maki H, Toyama K, Masamoto Y, Bujo C, Amiya E, Hatano M, Ono M, Komuro I, and Kurokawa M. Successful treatment of EBV-related lymphoproliferative disease after heart transplantation with autologous hematopoietic stem cell transplantation despite transient heart failure associated with engraftment syndrome. Annals of Hematology 100(4):1097-1100, 2021.
3. Oyama Y, Yasunaga M, Honda A, Maki H, Masamoto Y, Kobayashi T, Wakabayashi Y, Okugawa S, Moriya K, and Kurokawa M. Severe cellulitis caused by Achromobacter xylosoxidans after allogeneic hematopoietic stem cell transplantation. Journal of Infection and Chemotherapy 27(5): 770-772, 2021.
4. Sato M, Honda A, Maki H, Toyama K, Yamaguchi R, Ikeda M, Moriya K, and Kurokawa M. Successful treatment of pneumonia caused by multidrug-resistant Pseudomonas aeruginosa after allogeneic hematopoietic stem cell transplantation with colistin and amikacin inhalation therapy. Journal of Infection and Chemotherapy, 28(1): 91-94, 2022.
5. Ebisawa K, Honda A, Chiba A, Masamoto Y, Okazaki H, and Kurokawa M. High D-index during mobilization predicts poor mobilization of CD34+ cells after anti-lymphoma salvage chemotherapy. Journal of Clinical Apheresis, 37(1):4-12, 2022.
6. Kawahara Y, Morimoto A, Inagaki J, Koh K, Noguchi M, Goto H, Yoshida N, Cho Y, Hori T,

Hiwatari M, Kato K, Ogawa A, Hashii Y, Inoue M, Kato K, Atsuta Y, Kimura F, Kato M. Unrelated cord blood transplantation with myeloablative conditioning for pediatric acute lymphoblastic leukemia in remission: prognostic factors. Bone Marrow Transplant. 56(2): 357-367, 2021

Department of Endoscopy and Endoscopic Surgery

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Introduction and Organization

Department of Endoscopy and Endoscopic Surgery were 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 gastro-intestinal 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 2020-2021, 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.

	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
EGD*	11376	11840	11740	11874	11944	11490	11699 (2177)	11226 (2501)	8.906	10232
Colonoscopy	5688	6000	6043	6394	6814	5921	5530 (109)	5675 (329)	4,548	5619
Bronchoscopy	196	169	218	228	362	350	316	395	300	312
ERCP**	956	912	1035	946	1206	1137	1057	1314	1302	1166
EUS†	698	763	766	882	1084	1023	923	1059	711	847
Enteroscopy	282	375	396	310	86	304	138	151	74	23
Laryngoscopy	83	128	102	105	125	114	92	102	42	39
Colposcopy	365	404	327	295	417	430	414	392	333	364
Total	19644	20591	20627	21034	22038	20769	20169	20314	16226	18602

*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. Gotoda T, Akamatsu T, Abe S, Shimatani M, Nakai Y, Hatta W, Hosoe N, Miura Y, Miyahara R, Yamaguchi D, Yoshida N, Kawaguchi Y, Fukuda S, Isomoto H, Irisawa A, Iwao Y, Uraoka T, Yokota M, Nakayama T, Fujimoto K, Inoue H. Guidelines for sedation in gastroenterological endoscopy (second edition). Dig Endosc. 2021; 33(1):21-53.
2. Hakuta R, Kogure H, Nakai Y, Kawakami H, Maguchi H, Mukai T, Iwashita T, Saito T, Togawa O, Matsubara S, Hayashi T, Maetani I, Ito Y, Hasebe O, Itoi T, Hanada K, Isayama H. Unilateral versus bilateral endoscopic nasobiliary drainage and subsequent metal stent placement for unsectable malignant hilar obstruction: A Multicenter Randomized Controlled Trial. J Clin Med. 2021;10(2):206.
3. Saito K, Nakai Y, Isayama H, Yamamoto R, Kawakubo K, Kodama Y, Katanuma A, Kanno A, Itonaga M, Koike K. A prospective multicenter study of partially covered metal stents in patients receiving neoadjuvant chemotherapy for resectable and borderline resectable pancreatic cancer: BTS-NAC study. Gut Liver. 2021;15(1):135-141.
4. Niikura R, Fujishiro M, Nakai Y, Matsuda K, Kawahara T, Yamada A, Tsuji Y, Hayakawa Y, Koike K. International observational survey of the effectiveness of personal protective equipment during endoscopic procedures performed in patients with COVID-19. Digestion. 2021:1-9.
5. Hamada T, Nakai Y, Isayama H, Koike K. Antireflux metal stent for biliary obstruction: Any benefits? Dig Endosc. 2021;33(3):310-320.
6. Kogure H, Sato T, Nakai Y, Ishigaki K, Hakuta R, Saito K, Saito T, Takahara N, Hamada T, Mizuno S, Yamada A, Tada M, Isayama H, Koike K. Endoscopic management of pancreatic diseases in patients with surgically altered anatomy: clinical outcomes of combination of double-balloon endoscopy- and endoscopic ultrasound-guided interventions. Dig Endosc. 2021;33(3):441-450.
7. Sato T, Kogure H, Nakai Y, Kanai S, Ishigaki K, Hakuta R, Saito K, Saito T, Takahara N, Hamada T, Mizuno S, Yamada A, Isayama H, Koike K. Endoscopic treatment of hepaticojejunostomy anastomotic strictures using fully-covered metal stents. Dig Endosc. 2021;33(3):451-457.
8. Watanabe T, Nakai Y, Mizuno S, Hamada T, Kogure H, Hirano K, Akamatsu N, Hasegawa K,

Isayama H, Koike K. Prognosis of primary sclerosing cholangitis according to age of onset. J Hepatobiliary Pancreat Sci. 2021;28(12):1115-1120.

9. Hamada T, Oyama H, Nakai Y, Tada M , Koh H, Tateishi K, Arita J, Hakuta R, Ijichi H, Ishigaki K, Kawaguchi Y, Kogure H, Mizuno S, Morikawa T, Saito K, Saito T, Sato T, Takagi K, Takahara N, Takahashi R, Tanaka A, Tanaka M, Ushiku T, Hasegawa K, Koike K. ABO Blood Group and Risk of Pancreatic Carcinogenesis in Intraductal Papillary Mucinous Neoplasms. Cancer Epidemiol Biomarkers Prev. 2021;30(59): 1020-1028.
10. Ishigaki K, Nakai Y, Sasahira N, Sugimori K, Kitamura K, Iwai T, Matsubara S, Shimura K, Itoi T, Ryozawa S, Ushio J, Doi S, Imazu H, Maetani I, Isayama H, Acquire Study Group. A prospective multicenter study of endoscopic ultrasound-guided fine needle biopsy using a 22-gauge Franseen needle for pancreatic solid lesions. J Gastroenterol Hepatol. 2021;36(10) 2754-2761.
11. Nakai Y, Hamada T, Hakuta R, Sato T, Ishigaki K, Saito K, Saito T, Takahara N, Mizuno S, Kogure H, Koike K. A Meta-Analysis of Slow Pull versus Suction for Endoscopic Ultrasound-Guided Tissue Acquisition. Gut Liver 2021; 15(4):625-633.
12. Kogure H, Kato H, Kawakubo K, Ishiwatari H, Katanuma A, Okabe Y, Ueki T, Ban T, Hanada K, Sugimori K, Nakai Y, Isayama H. A Prospective Multicenter Study of "Inside Stents" for Biliary Stricture: Multicenter Evolving Inside Stent Registry (MEISteR). J Clin Med. 2021; 10(13):2936.
13. Hasegawa Y, Ijichi H, Saito K, Ishigaki K, Takami M, Sekine R, Usami S, Nakai Y, Koike K, Kubota N. Protein intake after the initiation of chemotherapy is an independent prognostic factor for overall survival in patients with unresectable pancreatic cancer: A prospective cohort study. Clin Nutr. 2021;40(7):4792-4798.
14. So H, Oh D, Takenaka M, Minaga K, Uemura S, Iwashita T, Saito T, Nakai Y, Kim S, Park D. Initial experience of endoscopic ultrasound-guided antegrade covered stent placement with long duodenal extension for malignant distal biliary obstruction (with video). J Hepatobiliary Pancreat Sci. 2021;28(12):1130-1137.
15. Sano M, Takahashi R Ijichi H, Ishigaki K, Yamada T, Miyabayashi K, Kimura G, Mizuno S, Kato H, Fujiwara H, Nakatsuka T, Tanaka Y, Kim J, Masugi Y, Morishita Y, Tanaka M, Ushiku T, Nakai Y, Tateishi K, Ishii Y, Isayama H, Moses H, Koike K. Blocking VCAM-1 inhibits pancreatic tumour progression and cancer-associated thrombosis/thromboembolism. Gut 2021;70(9):1713-1723.
16. Kurokawa R, Inui S, Tanishima T, Nakaya M, Kurokawa M, Ishida M, Gonoi W, Amemiya S, Nakai Y, Ishigaki K, Tateishi R, Koike K, Abe O. Incidence and computed tomography findings of lenvatinib-induced pancreatobiliary inflammation A single-center, retrospective study. Medicine. 2021;100(35):e27182.
17. Nakai Y, Smith Z, Chang K, Dua K. Advanced Endoscopic Techniques for the Diagnosis of Pancreatic Cancer and Management of Biliary and GastricOutlet Obstruction. Surg Oncol Clin N Am. 2021;30(4):639-656.
18. Nakai Y, Oyama H, Kanai S, Noguchi K, Sato T, Hakuta R, Ishigaki K, Saito K, Saito T, Hamada T, Takahara N, Mizuno S, Kogure H, Isayama H, Koike K. Double Guidewire Technique Using an Uneven Double Lumen Catheter for Endoscopic Ultrasound-Guided Interventions. Dig Dis Sci 2021;;66(5):1540-1547.

Department of Hemodialysis and Apheresis

Professor

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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. This new Center for Hemodialysis 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, which was developed collaboratively with Nihon Kohden Corp. 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 renal disease (ESRD).
2. Regular hemodialysis therapy for hospitalized ESRD patients. Please note that our center does not accept holiday dialysis.
3. Emergency hemodialysis and hemodiafiltration for ICU patients.
4. Plasmapheresis for neurodegenerative diseases, myasthenia gravis, dermatological disorders, waldenstrom macroglobulinemia, collagen diseases, TMA(TTP), and pre/post solid organ transplant patients.
5. LDL apheresis for familial hypercholesterolemia, nephrotic syndrome, and PAD patients.
6. White blood cell elimination therapy for inflamematory 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 ESRD.

Teaching activities

1. A systematic review course for M2 students, which covers clinical features, diagnosis, and evidence-based therapeutic strategies for acute kidney injury and acute renal failure.
2. Technical development course for medical engineers and nurses.
3. Tutorial course for clinical fellows applying to the speciality of blood purification therapy.
4. Exposure in hemodialysis & apheresis course to second year residents on request.
5. 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.

6. Our department takes main part in Critical Care Nephrology Course for educating young clinical researchers and fellows in collaboration with Department of Critical Care Medicine.

Research activities

1. Prognostic analysis for post-liver transplant patients received plasma exchange therapy.
2. Identification of prognostic factors in AKI/CRRT patients. AKI biomarkers and those clinical significance in ICU/CCU.
3. Associations between factors at the initiation of renal replacement therapy and prognosis in ESRD patients.
4. Identification of prognostic factors at initiation of peritoneal dialysis (PD), and at the onset of infectious complications in PD patients.
5. Elucidation of basic mechanisms in cardio-renal syndrome and intervention.
6. Pathophysiology of acute kidney injury and its applicability for renal regenerative study.
7. Renal biomarker to determine clinical actionability in CKD and type-2 DN.
8. The potentiality of urine biomarker tests for developing country [JICA-JST: Science and Technology Research Partnership for Sustainable Development].

References

1. 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. Epub 2021 Oct 14.
2. 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.
3. 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.
4. 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.
5. Kotani A, Oda Y, Hirakawa Y, Nakamura M, Hamasaki Y, Nangaku M. Peritoneal Dialysis-related Peritonitis Caused by Streptococcus oralis. ***Intern Med.*** 2021 May 22.
6. 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.
7. 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.
8. Matsuura R, Doi K, Hamasaki Y, Nangaku M. RRT Selection for AKI Patients With Critical Illness. ***Semin Nephrol.*** 2020 Sep;40(5):498-505.
9. 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.
10. 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.
11. 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.

12. 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.
13. 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.
14. 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.
15. 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.
16. 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.
17. Kimura C, Oki R, Hamasaki Y, Nangaku M. An Abscess Developing in an Old Subcutaneous Tunnel after Catheter Diversion. ***Intern Med.*** 2021 Mar 1;60(5):813-814.
18. Tanaka M, Ishibashi Y, Hamasaki Y, Kamijo Y, Idei M, Nishi T, Takeda M, Nonaka H, Nangaku M, Mise N. Ultrafiltration volume by once-weekly hemodialysis is a predictor of technique survival of combination therapy with peritoneal dialysis and hemodialysis. ***Ther Apher Dial.*** 2021 Feb; 25(1):82-87.
19. Tanaka M, Ishibashi Y, Hamasaki Y, Kamijo Y, Idei M, Nishi T, Takeda M, Nonaka H, Nangaku M, Mise N. Bioimpedance Spectroscopy-Based Fluid Status in Combined Dialysis Compared With Hemodialysis and Peritoneal Dialysis: A Cross-Sectional Study. ***Ther Apher Dial.*** 2020 Aug; 24(4): 373-379.
20. 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.
21. 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.
22. 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.
23. Tanaka M, Ishibashi Y, Hamasaki Y, Kamijo Y, Idei M, Kawahara T, Nishi T, Takeda M, Nonaka H, Nangaku M, Mise N. Hospitalization for Patients on Combination Therapy With Peritoneal Dialysis and Hemodialysis Compared With Hemodialysis. ***Kidney Int Rep.*** 2020 Jan 23;5(4): 468-474.
24. Tanaka M, Ishibashi Y, Hamasaki Y, Kamijo Y, Idei M, Kawahara T, Nishi T, Takeda M, Nonaka H, Nangaku M, Mise N. Health-related quality of life on combination therapy with peritoneal dialysis and hemodialysis in comparison with hemodialysis and peritoneal dialysis: A cross-sectional study. ***Perit Dial Int.*** 2020 Jan 17: 896860819894066.
25. 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.
26. 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.
27. Miyamoto Y, Iwagami M, Aso S, Yasunaga H, Matsui H, Fushimi K, Hamasaki Y, Nangaku M, Doi K. Association between intravenous contrast media exposure and non-recovery from dialysis-requiring septic acute kidney injury: a nationwide observational study. ***Intensive Care Med.*** 45, 1570-1579 (2019).

28. Hayase N, Doi K, Hiruma T, Matsuura R, Hamasaki Y, Noiri E, Nangaku M, Morimura N. Recombinant Thrombomodulin on Neutrophil Extracellular Traps in Murine Intestinal Ischemia-Reperfusion. ***Anesthesiology.*** 131, 866-882 (2019).
29. Miyamoto Y, Iwagami M, Aso S, Yasunaga H, Matsui H, Fushimi K, Hamasaki Y, Nangaku M, Doi K. Temporal change in characteristics and outcomes of acute kidney injury on renal replacement therapy in intensive care units: analysis of a nationwide administrative database in Japan, 2007-2016. ***Crit Care***. 23, 172 (2019).
30. Matsuura R, Doi K, Komaru Y, Miyamoto Y, Yoshida T, Isegawa T, Yoshimoto K, Yamashita T, Noiri E, Nangaku M. Endogenous Erythropoietin and Hepatic Dysfunction in Acute Kidney Injury Requiring Renal Replacement Therapy. ***Nephron.*** 142, 10-16(2019).
31. Yoshida T, Matsuura R, Komaru Y, Miyamoto Y, Yoshimoto K, Hamasaki Y, Noiri E, Morimura N, Nangaku M, Doi K. Kinetic estimated glomerular filtration rate as a predictor of successful continuous renal replacement therapy discontinuation. ***Nephrology (Carlton).*** 24, 287-293 (2019).
32. Miyamoto Y, Hamasaki Y, Matsumoto A, Doi K, Noiri E, Nangaku M. Prediction of immune-globulin M reduction via therapeutic dose of simple plasma exchange and double filtration plasmapheresis using membrane separation in patients with hyperviscosity syndrome caused by Waldenstrom macroglobulinemia. ***J Clin Apher.*** 33, 611-615 (2018).
33. Nakamura Y, Kurata Y, Hamasaki Y, Nangaku M. Extraperitoneal Placement of a Peritoneal Dialysis Catheter. ***Intern Med.*** 58, 147-148 (2019).
34. Isshiki R, Asada T, Sumida M, Hamasaki Y, Nangaku M, Noiri E, Doi K. Modest Impact of Serial Measurements of Acute Kidney Injury Biomarkers in an Adult Intensive Care Unit. ***Nephron.*** 139, 243-253 (2018).
35. Matsuura R, Srisawat N, Claure-Del Granado R, Doi K, Yoshida T, Nangaku M, Noiri E. Use of the Renal Angina Index in Determining Acute Kidney Injury. ***Kidney Int Rep.*** 3, 677-683 (2018)
36. Matsuura R, Komaru Y, Miyamoto Y, Yoshida T, Yoshimoto K, Isshiki R, Mayumi K, Yamashita T, Hamasaki Y, Nangaku M, Noiri E, Morimura N, Doi K. Response to different furosemide doses predicts AKI progression in ICU patients with elevated plasma NGAL levels. ***Ann Intensive Care.*** 8, 8 (2018)
37. Komaru Y, Inokuchi R, Ueda Y, Nangaku M, Doi K. Use of the anion gap and intermittent hemodialysis following continuous hemodiafiltration in extremely high dose acute-on-chronic lithium poisoning: A case report. ***Hemodial Int.*** 22, E15-E18 (2018)
38. Iwagami M, Yasunaga H, Matsui H, Horiguchi H, Fushimi K, Noiri E, Nangaku M, Doi K. Impact of end-stage renal disease on hospital outcomes among patients admitted to intensive care units: A retrospective matched-pair cohort study. ***Nephrology (Carlton).*** 22, 617-623 (2017)

University Hospital Medical Information Network (UMIN) Center

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Introduction and Organization

The University hospital Medical Information Network (UMIN) (the original name was the University Medical Information Network), was established in 1989. While general-use computer systems were implemented at all national university hospitals around the end of the Showa era (late 1980s), Dr. Shigekoto Kaihara, chair and professor at the Hospital Computer Center, University of Tokyo Hospital, led a project to connect these computer systems in a network in order to share information for better communication. Finally, the Ministry of Education, Culture, Sports, Science and Technology approved a budget to initiate the UMIN Center. 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 healthcare 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
ICDR: Individual Case Data Repository

■ Education: http://www.umin.ac.jp/education

CC-EPOC: Clinical Clerkship E-Portfolio of Clinical Training
EPOC2: E-Portfolio of Clinical Training 2
Debut: Dental Training Evaluation and Tabulation System
Web-QME: Medical Education Evaluation System
ARIA: Online Recruiting System for General Use

■ Medical Examination and Treatment
http://www.umin.ac.jp/uhosp/

- Intoxication database
- Medical supplies and materials database
- Classification for Nursing
- 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 Department of Health Communication for information about graduate and undergraduate education.

Research Activities

Please refer to Department of Health Communication for information about research activities.

References

Please refer to Department of Health Communication.

Department of Clinical Research Governance

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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 Child Psychiatry

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Assistant professor

Yosuke Eriguchi, M.D., Ph.D.

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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 38 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 2021, 9 psychiatrists and 4 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 2021 was 247, an increase of about 70 from the number of new patients last year, which had decreased due to the spread of COVID-19 infection. More than 35% of the new patients consisted of patients with ASD, ADHD or tic disorders. Out of 247 patients, children of elementary school age were 107, and children of junior high school age were 31. In other words, children of elementary or junior high school age were more than half of the patients. Number of preschool children was 94, 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.

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.

Effectiveness of a program of group cognitive behavior therapy for adults with high-functioning ASD is investigated in a randomized control trial.

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.

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.

Comprehensive Behavioral Intervention for Tics (CBIT) is provided for children and adolescents with Tourette syndrome, and investigation of its effectiveness is undertaken. We have also begun to develop psychoeducation materials via the iuternet that will lead to CBIT.

We continued survey of tics and related symptoms in community preschoolers and development of objective assessment for tics also.

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. Yagi T, Ando S, Usami S, Yamasaki S, Morita M, Kiyono T, Hayashi N, Endo K, Iijima Y, Morimoto Y, Kanata S, Fujikawa S, Koike S, Kano Y, Hiraiwa-Hasegawa M, Nishida A, Kasai K. Longitudinal Bidirectional Relationships Between Maternal Depressive/Anxious Symptoms and Children's Tic Frequency in Early Adolescence. Front Psychiatry, 12: 767571, 2021.
2. Kaji N, Ando S, Nishida A, Yamasaki S, Kuwabara H, Kanehara A, Satomura Y, Jinde S, Kano Y, Hiraiwa-Hasegawa M, Igarashi T, Kasai K. Children with special health care needs and mothers' anxiety/depression: Findings from the Tokyo Teen Cohort study. Psychiatry Clin Neurosci.,75(12): 394-400, 2021.
3. Eriguchi Y, Gu X, Aoki N, Nonaka M, Goto R, Kuwabara H, Kano Y, Kasai K. A 2-year longitudinal follow-up of quantitative assessment neck tics in Tourette's syndrome. PLoS One, 16(12): e0261560, 2021.
4. Okada N, Yamamoto Y, Yahata N, Morita S, Koshiyama D, Morita K, Sawada K, Kanata S, Fujikawa S, Sugimoto N, Toriyama R, Masaoka M, Koike S, Araki T, KanoY, Endo K, Yamasaki S, Ando S, Nishida A, Hiraiwa-Hasegawa M, Yokoyama C, Kasai K, Birth order and prosociality in the early adolescent brain. Sci Rep, 11(1): 21806, 2021.
5. Kimura Y, Iijima K, Takayama Y, Yokosako S, Kaneko Y, Omori M, Kaido T, Kano Y, Iwasaki M. Deep Brain Stimulation for Refractory Tourette Syndrome: Electrode Position and Clinical Outcome. Neurol Med Chir (Tokyo), 61(1): 33-39, 2021.
6. Kato Y, Kuwabara H, Okada T, Munesue T, Benner S, Kuroda M, Kojima M, Yassin W, Eriguchi Y, Kameno Y, Murayama C, Nishimura T, Tsuchiya K, Kasai K, Ozaki N, Kosaka H, Yamasue H. Oxytocin-induced increase in N,N-dimethylglycine and time course of changes in oxytocin efficacy for autism social core symptoms. Mol Autism, 12(1):15, 2021.
7. Kuru Y, Nishiyama T, Sumi S, Suzuki F, Shiino T, Kimura T, Hirai K, Kuroda M, Kamio Y, Kikuchi S. Practical applications of brief screening questionnaires for autism spectrum disorder in a psychiatry outpatient setting. Int J Methods Psychiatr Res, 30(2): e1857, 2021.

Tissue Bank

Director and Associate Professor

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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 suppy since 2018. Dissemination and educational activities for the advancement of tissue transplantation and trans-plantation medicine is our important mission. In this line of effort, starting 2020, 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.

Center for Epidemiology and Preventive Medicine

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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, and to 20 in April 2019, and to 22 in January 2021. 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 nine nurses, six assistant clerks, and one medical clerk.

Clinical activities

In addition to basic examinations, we provide ten optional examinations: 1) comprehensive cardiovascular examinations, 2) comprehensive cerebrovascular examinations, 3) check up 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 2021 was 8636 including 3022 in basic examinations, 543 in complete cardiovascular examinations, 682 in complete cerebrovascular examinations, 114 in check up for dementia, 391 in colorectal cancer screening, 660 in uterine cancer screening, 788 in breast cancer screening, 704 in lung cancer screening, 1236 in tumor marker diagnosis, 279 in estimation of gastric cancer risk, 217 in pancreatic cancer screening, and 14 in upper gastrointestinal endoscopy (later). Respiratory function test has been cancelled from March 31,2020 due to coronavirus.

One of the most important role 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 factor for the satisfaction of the examinees. In the FY 2021, we issued 1506 letters of referral to other departments in our hospital and 50 to other hospitals.

We have expanded our public relations efforts. We renewed brochures and 15,000 brochures were delivered during the FY 2021.

We also renewed posters which were placed 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. We have updated our original

website (https://www.todai-yobouigaku-dock.jp/) and offering up-to-date information to the examinees.

The University of Tokyo Hospital is aiming to establish the Center for International Preventive Medicine, and we provide full cooperation to prepare for establishment.

References

Academic Papers in English

1. Fukuda K, Matsuzaki H, Mikami Y, Makita K, Miyakawa K, Miyashita N, Hosoki K, Ishii T, Noguchi S, Urushiyama H, Horie M, Mitani A, Yamauchi Y, Shimura E, Nakae S, Saito A, Nagase T, Hiraishi Y. A mouse model of asthma-chronic obstructive pulmonary disease overlap induced by intratracheal papain. Allergy. 2021 Jan;76(1):390-394.
2. Sugita J, Fujiu K, Nakayama Y, Matsubara T, Matsuda J, Oshima T, Liu Y, Maru Y, Hasumi E, Kojima T, Seno H, Asano K, Ishijima A, Tomii N, Yamazaki M, Kudo F, Sakuma I, Nagai R, Manabe I, Komuro I. Cardiac macrophages prevent sudden death during heart stress. Nat Commun. 2021 Mar 26;12(1):1910.
3. Sakaguchi Y, Tsuji Y, Ushiku T, Kubota D, Sato J, Obata M, Cho R, Nagao S, Sakuma N, Tamura N, Miura Y, Fukagawa K, Ohki D, Mizutani H, Takeuchi C, Takahashi Y, Minatsuki C, Niimi K, Yamamichi N, Koike K. The natural history of sporadic non-ampullary duodenal epithelial tumors: Can we wait and see? DEN open. 2021 Apr 21;1(1):e9.
4. Kirita K, Kodaka Y, Shibata Y, Ueki N, Agawa S, Yamawaki H, Niikura R, Yamamichi N, Izumi K, Hojo M, Maruyama K, Yamamoto T, Gudis K, Watanabe M, Kaise M, Iwakiri K, Futagami S. Impact of clinical characteristics of colonic diverticular bleeding in extremely elderly patients treated with direct oral anti-coagulant drugs: a retrospective multi-center study. J Clin Biochem Nutr. 2021 Sep;69(2):222-228.
5. Yamamichi N, Shimamoto T, Hirano C, Takahashi Y, Minatsuki C, Takeuchi C, Takahashi M, Sakaguchi Y, Tsuji Y, Niimi K, Wada R, Mitsushima T, Koike K. Clinicopathological features and prognosis of developed gastric cancer based on the diagnosis of mucosal atrophy and enlarged folds of stomach by double-contrast upper gastrointestinal barium X-ray radiography. Clin J Gastroenterol. 2021 Aug;14(4):947-954.
6. Yokota J, Fujiu K, Oshima T, Matsubara TJ, Matsuda J, Shimizu Y, Hasumi E, Kojima T, Doi K, Komuro I. Pseudo-elevation of conduction system pacing threshold through parallel connection of an intracardiac electrogram recording system. J Cardiovasc Electrophysiol. 2021 Aug;32(8):2329-2332.
7. Oshima T, Fujiu K, Matsunaga H, Matsuda J, Matsubara T, Saga A, Yoshida Y, Shimizu Y, Hasumi E, Oguri G, Kojima T, Komuro I. Uninterrupted Direct Oral Anticoagulants Without a Change in Regimen for Catheter Ablation for Atrial Fibrillation Is an Acceptable Protocol Circ Rep. 2021 Jul 30;3(9):481-487.
8. Miura Y, Tsuji Y, Cho R, Fujisawa A, Fujisawa M, Kamata H, Yoshikawa Y, Yamamichi N, Sakai T, Koike K. The feasibility of a novel injectable hydrogel for protecting artificial gastrointestinal ulcers after endoscopic resection: an animal pilot study. Sci Rep. 2021 Sep 16;11(1):18508.
9. Mehrazad Saber Z, Takeuchi Y, Sawada Y, Aita Y, Ho MH, Karkoutly S, Tao D, Katabami K, Ye C, Murayama Y, Shikama A, Masuda Y, Izumida Y, Miyamoto T, Matsuzaka T, Sugasawa T, Takekoshi K, Kawakami Y, Shimano H, Yahagi N. High protein diet-induced metabolic changes are transcriptionally regulated via KLF15-dependent and independent pathways. Biochem Biophys Res Commun. 2021 Dec 10;582:35-42.
10. Kamon T, Kaneko H, Itoh H, Kiriyama H, Mizuno Y, Morita H, Takeda N, Yamamichi N, Komuro I. Possible Gender Difference in the Association Between Abdominal Obesity, Chronic Inflammation, and Preclinical Atherosclerosis in the General Population. Int Heart J. 2021;62(4):837-842.
11. Hasumi E, Fujiu K. Tripartite Left Bundle Branch Area Pacing. Int Heart J. 2021;62(1):1-3.
12. Takeuchi Y, Yahagi N, Aita Y, Mehrazad-Saber Z, Ho MH, Huyan Y, Murayama Y, Shikama A, Masuda Y, Izumida Y, Miyamoto T, Matsuzaka T, Kawakami Y, Shimano H. FoxO-KLF15 pathway switches the flow of macronutrients under the

control of insulin. iScience. 2021 Nov 15;24(12): 103446.

International conferences

1. Yamamichi N. Gastric Cancer Screening in Japan. KCA-DDF Joint Symposium. (2021/6/18, WEB congress)
2. Nishikawa T, Kurano M, Ikeda H, Yamamichi N, Yatomi Y, Koike K. Lysophosphatidylserine may be involved in liver fibrosis. AASLD2021. (2021/11/12-15)

Department of Pain and Palliative Medicine

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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 two months (or * for one month)

- Program to acquire basic knowledge and practice of palliative care for targeting all junior residents. * Only in "Comprehensive Internal Medicine" selection.

The training course (selection) for four or eight months

- Program to acquire basic knowledge, practice, and skills of communication for doctors who need to be clinical oncologists or pain and palliative care specialists.

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.
- In the course for four and eight months, 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. Mietani K, et al. Elevateed neuron-specific enolase level is associated with postoperative delirium and detection of phosphorylated neurofilament heavy subunit: A prospective observational study. *PLoS ONE 2021; 16: e0259217*
2. The OSCIS investigators. Effect of early vs delayed surgery on motor recovery in incomplete cervical spinal cord injury with pre-existing cervical stenosis: a randomized clinical trial. *JAMA Network Open 2021; 4: e2133604*
3. Inoue R, et al. Capecitabine-induced hand-foot syndrome does not emerge in the complex regional pain syndrome-affected limb: Case Report. *Mol Clin Oncol 2021; 15: 254*
4. Kato K, et al. Development of a severity discrimination scale based on physical quality of life for patients with chronic pain. *J Orthop Sci 2021; 26: 1124-9*
5. Osumi M, et al. Fear of movement-related pain disturbs cortical preparatory activity after becoming aware of motor intention. *Behav Brain Res 2021; 411: 113379*
6. Osumi M, et al. Pain quality of thermal grill illusion is similar to that of central neuropathic pain rather than peripheral neuropathic pain. *Scand J Pain 2021; 22: 40-7*
7. Tsuchida R, et al. Genetic polymorphisms of lysophosphatidic acid receptor 1 are associated with the onset of taxane-induced peripheral neuropathy. *Br J Anaesth 2021; 127: e43-6*
8. Sumitani M. Time to act for reappraising the educational system for universal access to opioid analgesics, for quality palliative care and cancer-related pain relief in East Asian countries. *Lancet Regional Health – Western Pacific 2021; 16: 100270*
9. Saita K, et al. Exponential correlations among neuropathic components, pain intensity and catastrophic thoughts in patients with musculoskeletal pain disorder. *Curr Med Res Opin 2021; 37: 1341-8*
10. Ikeda K, et al. Required research activities to overcome addiction problems in Japan. *Taiwan J Psychiatr 2021; 35: 6-11*
11. Uranbileg B, et al. Inhibition of autotaxin activity ameliorates neuropathic pain derived from lumbar spinal stenosis. *Scientific Reports 2021; 11: 3984*
12. Ando M, et al. Tele virtual reality-based peer support programme for cancer patients: a

preliminary feasibility and acceptability study. *Br J Cancer Res 2021; 3: 443-8*

13. Nagata K, et al. Diabetes is associated with greater leg pain and worse patient-reported outcomes at one year after lumbar spine surgery. *Scientific Reports 2021; 11: 8142*
14. Owada H, et al. Peripheral nerve field stimulation successfully manages axial pain after posterior cervical spine surgery: case report. *Ann Palliat Med 2021; 10: 579-96*
15. Nishi Y, et al. Kinematic change in goal-directed movements in a fear-conditioning paradigm. *Scientific Reports 2021; 11: 11162*
16. Kaizu M, Komatsu H, Yamauchi H, et al. Characteristics of taste alterations in people receiving taxane-based chemotherapy and their association with appetite, weight and quality of life. *Supp Care Cancer 2021; 29: 5103-14*

(And, 18 Japanese articles)

Department of Disaster Medical Management

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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 April 2017, Professor Dr. Naoto Morimura was assigned the post as the fourth 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

As educational activities inside and outside of the University, we are holding and teaching MIMMS, Major Incident Medical Management and Support, courses accredited by English ALSG, Advanced Life Support Group, regularly for the purpose of developing leadership of health care professionals who can provide ideal medical care in times of disaster.

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.

Other than that, we are holding outside research groups and cooperating for building up a functional emergency medical system at the time of disaster.

References

1. Toida C, Muguruma T, Gakumazawa M, Shinohara M, Abe T, Takeuchi I, Morimura N. Age- and Severity-Related In-Hospital Mortality Trends and Risks of Severe Traumatic Brain Injury in Japan: A Nationwide 10-Year Retrospective Study. J Clin Med. 2021 Mar 4;10(5): 1072.
2. Toida C, Muguruma T, Gakumazawa M, Shinohara M, Abe T, Takeuchi I, Morimura N. Correlation between Hospital Volume of Severely Injured Patients and In-Hospital Mortality of Severely Injured Pediatric Patients in Japan: A Nationwide 5-Year Retrospective Study. J Clin Med. 2021 Apr 1;10(7):1422.
3. Hirayama I, Doi K, Yamamoto M, Toida C, Morimura N. Evaluation of Autonomous Actions on Bystander-Initiated Cardiopulmonary Resuscitation and Public Access Defibrillation in Tokyo. Int Heart J. 2021 Jul 30;62(4):879-884.

International Medical Center

Director and Associate Professor

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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. Starting last year, International Continuous Professional Development Program has been introduced, attracting multiple groups from around the globe for learning experience at 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.

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

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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 order to dispel the "too early, cold, unappetizing" reputation of hospital meals.

In 1991, the name of the food service section was changed to the "Department of Nutrition Management", a change that had a long been sought by nationwide national-university-hospital managerial dietitian staff members. 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, as a result of a partial revision of the National Health Insurance Act, 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 Exibit 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.

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 2021, nutritional guidance of inpatients and outpatients increased upto3648 instances for inpatients and 6916 instances for outpatients. Nutritional guidance for malignant tumor patients was performed for 822 instances.

The Center is also proactively cooperating with several departments in the hospital. In 2021, perioperative guidance was 91 instances, diabetes and dialysis prevention guidance for outpatients was 141 instances, dietary management with palliative care was 339 instances, nutritional guidance for outpatient chemotherapy was 161 instances, nutritional guidance at the preventive medicine center was 60 instances. In addition, the provision of inpatient nutrition information was 61 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. 260 rounds were performed and 204 instances were calculated in 2021.

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. Due to the COVID-19 pandemic, these programs accepting external trainee were cancelled in 2020-2021.

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. 106 medical students at M4 grade participated in the two-day practice course in 2021.

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, with total 546 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. Nakatsuka T, Tateishi K, Kato H, Fujiwara H, Yamamoto K, Kudo Y, Nakagawa H, Tanaka Y, Ijichi H, Ikenoue T, Ishizawa T, Hasegawa K, Tachibana M, Shinkai Y, Koike K. Inhibition of histone methyltransferase G9a attenuates liver cancer initiation by sensitizing DNA-damaged hepatocytes to p53-induced apoptosis. Cell Death Dis. 12:99, 2021.
2. Yamazaki T, Inada S, Sawada M, Sekine R, Kubota N, Fukatsu K, Yoshiuchi K. Diets with high carbohydrate contents were associated with refeeding hypophosphatemia: A retrospective study in Japanese inpatients with anorexia nervosa. Int J Eat Disord. 54:88-94, 2021.
3. Tanaka Y, Shimanaka Y, Caddeo A, Kubo T, Mao Y, Kubota T, Kubota N, Yamauchi T, Mancina RM, Baselli G, Luukkonen P, Pihlajamäki J, Yki-Järvinen H, Valenti L, Arai H, Romeo S, Kono N. LPIAT1/MBOAT7 depletion increases triglyceride synthesis fueled by high phosphatidylinositol turnover. Gut. 70:180-193, 2021.

4. Aihara M, Kubota N, Minami T, Shirakawa R, Sakurai Y, Hayashi T, Iwamoto M, Takamoto I, Kubota T, Suzuki R, Usami S, Jinnouchi H, Aihara M, Yamauchi T, Sakata T, Kadowaki T. Association between tear and blood glucose concentrations: Random intercept model adjusted with confounders in tear samples negative for occult blood. J Diabetes Investig. 12:266-276, 2021.
5. Saito K, Nakai Y, Takahara N, Ishigaki K, Suzuki Y, Inokuma A, Noguchi K, Kanai S, Sato T, Hakuta R, Saito T, Hamada T, Mizuno S, Kogure H, Ijichi H, Tateishi K, Koike K. A retrospective comparative study of S-IROX and modified FOLFIRINOX for patients with advanced pancreatic cancer refractory to gemcitabine plus nab-paclitaxel. Invest New Drugs. 39:605-613, 2021.
6. Sakurai Y, Kubota N, Yamauchi T, Kadowaki T. Role of Insulin Resistance in MAFLD. Int J Mol Sci. 22:4156, 2021.
7. Hamada T, Oyama H, Nakai Y, Tada M, Koh H, Tateishi K, Arita J, Hakuta R, Ijichi H, Ishigaki K, Kawaguchi Y, Kogure H, Mizuno S, Morikawa T, Saito K, Saito T, Sato T, Takagi K, Takahara N, Takahashi R, Tanaka A, Tanaka M, Ushiku T, Hasegawa K, Koike K. ABO Blood Group and Risk of Pancreatic Carcinogenesis in Intraductal Papillary Mucinous Neoplasms. Cancer Epidemiol Biomarkers Prev. 30:1020-1028, 2021.
8. Kubota N, Kubota T, Kadowaki T. Midlobular zone 2 hepatocytes: A gatekeeper of liver homeostasis. Cell Metab. 33:855-856, 2021.
9. Watanabe D, Murakami H, Ohno H, Tanisawa K, Konishi K, Todoroki-Mori K, Tsunematsu Y, Sato M, Ogata Y, Miyoshi N, Kubota N, Kunisawa J, Wakabayashi K, Kubota T, Watanabe K, Miyachi M. Stool pattern is associated with not only the prevalence of tumorigenic bacteria isolated from fecal matter but also plasma and fecal fatty acids in healthy Japanese adults. BMC Microbiol. 21: 196, 2021.
10. Hasegawa Y, Ijichi H, Saito K, Ishigaki K, Takami M, Sekine R, Usami S, Nakai Y, Koike K, Kubota N. Protein intake after the initiation of chemotherapy is an independent prognostic factor for overall survival in patients with unresectable pancreatic cancer: A prospective cohort study. Clin Nutr. 40:4792-4798, 2021.
11. Watkins A, Fukatsu K, Higashizono K, Watanabe T, Noguchi M, Tominaga E, Murakoshi S, Yasuhara H. Influence of a Low-Carbohydrate High-Fat Diet on Peritoneal Inflammation, Cancer-Associated Lymphocytes, and Survival in a Murine Carcinomatous Peritonitis Model. JPEN J Parenter Enteral Nutr. 45:1293-1301, 2021.
12. Hayashi T, Kubota T, Mariko I, Takamoto I, Aihara M, Sakurai Y, Wada N, Miki T, Yamauchi T, Kubota N, Kadowaki T. Lack of Brain Insulin Receptor Substrate-1 Causes Growth Retardation, With Decreased Expression of Growth Hormone-Releasing Hormone in the Hypothalamus. Diabetes. 70:1640-1653, 2021.
13. Furuzono S, Kubota T, Taura J, Konishi M, Naito A, Tsutsui M, Karasawa H, Kubota N, Kadowaki T. A xanthene derivative, DS20060511, attenuates glucose intolerance by inducing skeletal muscle-specific GLUT4 translocation in mice. Commun Biol. 4:994, 2021.
14. Sano M, Takahashi R, Ijichi H, Ishigaki K, Yamada T, Miyabayashi K, Kimura G, Mizuno S, Kato H, Fujiwara H, Nakatsuka T, Tanaka Y, Kim J, Masugi Y, Morishita Y, Tanaka M, Ushiku T, Nakai Y, Tateishi K, Ishii Y, Isayama H, Moses HL, Koike K. Blocking VCAM-1 inhibits pancreatic tumour progression and cancer-associated thrombosis/thromboembolism. Gut. 70:1713-1723, 2021.
15. Ochiai T, Sano T, Nagayama T, Kubota N, Kadowaki T, Wakabayashi T, Iwatsubo T. Differential involvement of insulin receptor substrate (IRS)-1 and IRS-2 in brain insulin signaling is associated with the effects on amyloid pathology in a mouse model of Alzheimer's disease. Neurobiol Dis. 159:105510, 2021.
16. Ishihama S, Yoshida S, Yoshida T, Mori Y, Ouchi N, Eguchi S, Sakaguchi T, Tsuda T, Kato K, Shimizu Y, Ohashi K, Okumura T, Bando YK, Yagyu H, Wettschureck N, Kubota N, Offermanns S, Kadowaki T, Murohara T, Takefuji M. LPL/AQP7/GPD2 promotes glycerol metabolism under hypoxia and prevents cardiac dysfunction during ischemia. FASEB J. 35:e22048, 2021.

17. Jinnouchi T, Sakurai Y, Miyoshi K, Koizumi C, Waki H, Kubota N, Yamauchi T. Chronic Intestinal Pseudo-obstruction with Mitochondrial Diseases. Intern Med. 61:469-474, 2021.
18. Kato H, Tateishi K, Fujiwara H, Nakatsuka T, Yamamoto K, Kudo Y, Hayakawa Y, Nakagawa H, Tanaka Y, Ijichi H, Otsuka M, Iwadate D, Oyama H, Kanai S, Noguchi K, Suzuki T, Sato T, Hakuta R, Ishigaki K, Saito K, Saito T, Takahara N, Kishikawa T, Hamada T, Takahashi R, Miyabayashi K, Mizuno S, Kogure H, Nakai Y, Hirata Y, Toyoda A, Ichikawa K, Qu W, Morishita S, Arita J, Tanaka M, Ushiku T, Hasegawa K, Fujishiro M, Koike K. MNX1-HNF1B Axis Is Indispensable for Intraductal Papillary Mucinous Neoplasm Lineages. Gastroenterology. Epub 2021 Dec 22.

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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^{TM} NCC Oncopanel System, FoundationOne® CDx Cancer Genomic Profililng) were approved by PMDA in June, 2019. FoundationOne® Liquid CDx Cancer Genomic Profililng will be 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 room (Room 202) is specifically allocated in the outpatient clinic for genomic medicine in cancer (twice weekly).

Publications

1. Iwasaki A, Shinozaki-Ushiku A, Kunita A, Yamazawa S, Sato Y, Yamashita H, Fukayama M, Seto Y, Ushiku T: Human Leukocyte Antigen Class I Deficiency in Gastric Carcinoma: An Adaptive Immune Evasion Strategy Most Common in Microsatellite Instable Tumors. ***Am J Surg Pathol*** 45:1213-1220,2021.
2. Nagano M, Kohsaka S, Hayashi T, Ueno T, Kojima S, Shinozaki-Ushiku A, Morita S, Tsuda M, Tanaka S, Shinohara T, Omori Y, Sugaya F, Kato H, Narita Y, Nakajima J, Suzuki K, Takamochi K, Mano H: Comprehensive molecular profiling of pulmonary pleomorphic carcinoma. ***NPJ Precis Oncol*** 5:57,2021.
3. Sato A, Tanabe M, Tsuboi Y, Niwa T, Shinozaki-Ushiku A, Seto Y, Murakami Y: Circulating

Tumor DNA Harboring the BRAF(V600E) Mutation May Predict Poor Outcomes of Primary Papillary Thyroid Cancer Patients. ***Thyroid*** 31: 1822-1828,2021.

4. Kato S, Kubota Y, Sekiguchi M, Watanabe K, Shinozaki-Ushiku A, Takita J, Hiwatari M: KMT2A-rearranged diffuse large B-cell lymphoma in a child: a case report and molecular characterization. ***Pediatr Hematol Oncol*** 38: 281-289,2021.
5. Sunami K, Naito Y, Aimono E, Amano T, Ennishi D, Kage H, Kanai M, Komine K, Koyama T, Maeda T, Morita S, Sakai D, Kohsaka S, Tsuchihara K, Yoshino T: Correction to: The initial assessment of expert panel performance in core hospitals for cancer genomic medicine in Japan. ***Int J Clin Oncol*** 26:1007,2021.
6. Sunami K, Naito Y, Aimono E, Amano T, Ennishi D, Kage H, Kanai M, Komine K, Koyama T, Maeda T, Morita S, Sakai D, Kohsaka S, Tsuchihara K, Yoshino T: The initial assessment of expert panel performance in core hospitals for cancer genomic medicine in Japan. ***Int J Clin Oncol*** 26:443-449,2021.
7. Ikushima H, Hiraishi Y, Toriumi K, Ando T, Tamiya H, Ishida J, Amano Y, Kage H, Tanaka G, Nagase T: Multiple cerebral infarctions in ROS1-rearranged lung adenocarcinoma. ***Respirol Case Rep*** 9:e0831,2021.
8. Naito Y, Aburatani H, Amano T, Baba E, Furukawa T, Hayashida T, Hiyama E, Ikeda S, Kanai M, Kato M, Kinoshita I, Kiyota N, Kohno T, Kohsaka S, Komine K, Matsumura I, Miura Y, Nakamura Y, Natsume A, Nishio K, Oda K, Oda N, Okita N, Oseto K, Sunami K, Takahashi H, Takeda M, Tashiro S, Toyooka S, Ueno H, Yachida S, Yoshino T, Tsuchihara K: Clinical practice guidance for next-generation sequencing in cancer diagnosis and treatment (edition 2.1). ***Int J Clin Oncol*** 26:233-283,2021.
9. Ebihara T, Nagatomo T, Sugiyama Y, Tsuruoka T, Osone Y, Shimura M, Tajika M, Matsuhashi T, Ichimoto K, Matsunaga A, Akiyama N, Ogawa-Tominaga M, Yatsuka Y, Nitta KR, Kishita Y, Fushimi T, Imai-Okazaki A, Ohtake A, Okazaki Y, Murayama K: Neonatal-onset mitochondrial disease: clinical features, molecular diagnosis and prognosis. ***Arch Dis Child Fetal Neonatal Ed*** 107:329-334,2022.
10. Akiyama N, Shimura M, Yamazaki T, Harashima H, Fushimi T, Tsuruoka T, Ebihara T, Ichimoto K, Matsunaga A, Saito-Tsuruoka M, Yatsuka Y, Kishita Y, Kohda M, Namba A, Kamei Y, Okazaki Y, Kosugi S, Ohtake A, Murayama K: Prenatal diagnosis of severe mitochondrial diseases caused by nuclear gene defects: a study in Japan. ***Sci Rep*** 11:3531,2021.

BioResource Center

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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 BiorResource Center Project was also approved by 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 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 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.

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 and pediatric in the future.

Teaching activities

Research activities

In FY2021, we focused on the establishment of the

center. We hope to expand our activities in education and research in the coming year.

References

None

Clinical Research Promotion Center

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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 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 IRB to ensure transparency of clinical research. IRB for evaluating 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 core clinical research 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.

In addition, in order to enhance the functions in which the Clinical Research Support Center was widely involved in 2015, Education and Training Division, Clinical Trial Implementation Division and University Hospital Network Promotion Division were established outside the unit. In fiscal year 2017, we further integrated safety information functions of the Site Coordinating Unit and the Central Coordinating Unit and established a new Safety Information Management Division out the unit. The division remaining in the Site Coordinating Unit was named as the Investigational Drug Management Division. Furthermore, Consultation Division was relocated outside the unit. In 2017, The Regulatory Strategy Division was also established within the Central Coordinating Unit. In order to comply with the Clinical Trials Act that was enforced in April 2018, we established Clinical Research Site Secretariat, enacted general and individual rules to respond to the act and started operation.

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) Support for physicians and others in formulating development strategies for clinical trials, advice on study design, and support for pharmaceutical affairs, funding, intellectual property, and industry-academia collaborations; (3) Support for the promotion of investigator-initiated clinical trials conducted by physicians and others; (4) Monitoring, data management and data analysis required to ensure the quality of investigator-initiated clinical studies; (5) Collecting and reporting on safety information related to investigator-initiated clinical trials and providing advice to physicians and others on the safe conduct of clinical 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 physicians and others 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 and Personal Information Management Department>

The department is responsible for: (1) Management of safety reports and collection and reporting of safety information; (2) Management of personal information.

<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 physicians and others who wish to conduct clinical research; (5) Management of the progress of clinical research conducted by physicians and others and supported by the Center.

<Network Promotion Department>

The department is responsible for: (1) Secretariat duties for the National University Hospital Clinical Research Promotion Initiative joined by 45 hospitals of 42 national universities; (2) Secretariat duties for the University Hospital Clinical Trial Alliance joined by 8 universities and 9 hospitals in the Kanto-Koshinetsu region, a network of university hospitals engaged in clinical research.

<Clinical Trials Patient Counseling Department>

The department is responsible for providing consultation and public relations services for patients who would like to use advanced medical care.

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). To further improve the quality of these supports we decided to adopt ICH-GCP guidance and complied with the guidelines, procedure manuals, styles and guidance etc. 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. Moreover, since clinical departments were placed in charge of monitoring and data management of all exploratory studies, 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. One of the major achievements is the investigator-initiated clinical trial of the pediatric ventricular assist device; the trial was initiated in February 2012, applied for regulatory approval in November 2014, and marketing approval was received in June 18, 2015.

Since its establishment in May 2012, the Phase 1 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. UHCT ACReSS can easily be customized by researchers. Currently, we are considering cloud computing and expanding its use to researchers other than Alliance members.

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.

Activities between the UHCT Alliance and the University of Tokyo Translational Research (TR) based regional network started in 2015, as seeds development project of Alliance members.

<National University Hospital Clinical Research Initiative>

In October 2012, we launched 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. In 2016, the curriculum was provided to each university hospital by the National University Hospital Council of Japan. 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.

Education and Training Division was established in 2015 and since then 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 2020, the Center was involved in scientific meetings, which include The Japan Society of Clinical Pharmacology and Therapeutics, Conference on CRC and Clinical Trials, etc. As for publications such as academic papers, 30 papers were produced (29 papers in English and 1 paper in Japanese).

Publications

1) Sotomi Y, Kozuma K, Kashiwabara K, Higuchi Y, Ando K, Morino Y, Ako J, Tanabe K, Muramatsu T, Nakazawa G, Hikoso S, Sakata Y; OPTIMA-AF Investigators. Randomised controlled trial to investigate optimal antithrombotic therapy in patients with non-valvular atrial fibrillation undergoing percutaneous coronary intervention: a study protocol of the OPTIMA-AF trial. BMJ Open. 11, e048354, 2021
2) Ebata S, Yoshizaki A, Fukasawa T, Yoshizaki-Ogawa A, Asano Y, Kashiwabara K, Oba K, Shinichi Sato. Increased red blood cell distribution width in the first year after diagnosis predicts worsening of systemic sclerosis-associated interstitial lung disease at 5 years: a pilot study. Diagnostics. 11, article 2274, 2021
3) Kaibori M, Yoshii K, Kashiwabara K, Kokudo T, Hasegawa K, Izumi N, Murakami T, Kudo M, Shiina S, Sakamoto M, Nakashima O, Matsuyama Y, Eguchi S, Yamashita T, Takayama T, Kokudo N, Kubo S. Impact of hepatitis C virus on survival in patients undergoing resection of intrahepatic cholangiocarcinoma: Report of a Japanese nationwide survey. Hepatology Research. 51, 890–901, 2021
4) Ebata S, Yoshizaki A, Oba K, Kashiwabara K, Ueda K, Uemura Y, Watadani T, Fukasawa T, Miura S, Yoshizaki-Ogawa A, Asano Y, Okiyama N, Kodera M, Hasegawa M, Sato S. Safety and efficacy of rituximab in systemic sclerosis (DESIRES): a double-blind, investigator-initiated, randomised, placebo-controlled trial. Lancet Rheumatology. 3, E489–E497, 2021
5) Koyanagi H, Kitamura A, Nakagami G, Kashiwabara K, Sanada H, Sugama J. Local wound management factors related to biofilm reduction in the pressure ulcer: A prospective

observational study. Japan Journal of Nursing Science. 18, e12394, 2021

6) Umeda M, Ota Y, Kashiwabara K, Hayashi N, Naito M, Yamashita T, Mukai H, Nakatsukasa K, Amemiya T, Watanabe K, Hata H, Kikawa Y, Taniike N, Yamanaka T, Mitsunaga S, Nakagami K, Adachi M, Kondo N, Shibuya Y, Niikura N. Oral care and oral assessment guide in breast cancer patients receiving everolimus and exemestane: subanalysis of a randomized controlled trial (Oral Care-BC). Annals of Translational Medicine. 9, 535, 2021
7) Tateishi R, Matsumura T, Okanoue T, Shima T, Uchino K, Fujiwara N, Senokuchi T, Kon K, Sasako T, Taniai M, Kawaguchi T, Inoue H, Watada H, Kubota N, Shimano H, Kaneko S, Hashimoto E, Watanabe S, Shiota G, Ueki K, Kashiwabara K, Matsuyama Y, Tanaka H, Kasuga M, Araki E, Koike K, and LUCID study investigators. Hepatocellular carcinoma development in diabetic patients: a nationwide survey in Japan. Journal of Gastroenterology. 56, 261–273, 2021
8) Nakatsukasa K, Niikura N, Kashiwabara K, Amemiya T, Watanabe K, Hata H, Kikawa Y, Taniike N, Yamanaka T, Mitsunaga S, Nakagami K, Adachi M, Kondo N, Shibuya Y, Hayashi N, Naito M, Yamashita T, Umeda M, Mukai H, Ota Y. Secondary endpoints analysis in patients with estrogen receptor-positive metastatic breast cancer treated with everolimus and exemestane enrolled in Oral Care-BC. BMC Cancer. 21, 34, 2021
9) Niikura R, Aoki T, Kojima T, Kawahara T, Yamada A, Nakamura H, Inoue K, Morikoshi E, Migita R, Shimizu T, Kojima T, Koike K. Natural history of upper and lower gastrointestinal bleeding in hemodialysis patients: A dual-center long-term cohort study. J Gastroenterol Hepatol. 36:112-117, 2021
10) Bae SK, Akamatsu N, Ichida A, Maki H, Nishioka Y, Kawahara T, Hoshikawa M, Nagata R, Mihara Y, Kawaguchi Y, Ishizawa T, Arita J, Kaneko J, Tamura S, Hasegawa K. Risk factors for hepatitis B virus recurrence after living donor liver transplantation: A 22-year experience at a single center. Biosci Trends. 14:443-449, 2021
11) Kurokawa R, Hagiwara A, Amemiya S, Gonoi W, Fujita N, Kurokawa M, Yamaguchi H, Nakai Y, Ota Y, Baba A, Kawahara T, Abe O. Imatinib-induced pancreatic hypertrophy in patients with gastrointestinal stromal tumor: Association with overall survival. Pancreatology. 21:246-252, 2021
12) Adachi Y, Kiyosue A, Ando J, Kawahara T, Kodera S, Minatsuki S, Kikuchi H, Inaba T, Kiriyama H, Hirose K, Shinohara H, Saito A, Fujiwara T, Hara H, Ueda K, Sakakura K, Hatano M, Harada M, Takimoto E, Akazawa H, Morita H, Momomura SI, Fujita H, Komuro I. Factors associated with left ventricular reverse remodelling after percutaneous coronary intervention in patients with left ventricular systolic dysfunction. Sci Rep. 11:239, 2021
13) Fujimoto C, Kawahara T, Kinoshita M, Ichijo K, Oka M, Kamogashira T, Sugasawa K, Yamasoba T, Iwasaki S. Minimally important differences for subjective improvement in postural stability in patients with bilateral vestibulopathy. Neurosci Lett. 747:135706, 2021
14) Arai J, Niikura R, Hayakawa Y, Kawahara T, Honda T, Hasatani K, Yoshida N, Nishida T, Sumiyoshi T, Kiyotoki S, Ikeya T, Arai M, Suzuki N, Tsuji Y, Yamada A, Kawai T, Koike K. Use of Antibiotics and Probiotics Reduces the Risk of Metachronous Gastric Cancer after Endoscopic Resection. Biology (Basel). 10:455, 2021
15) Niikura R, Fujishiro M, Nakai Y, Matsuda K, Kawahara T, Yamada A, Tsuji Y, Hayakawa Y, Koike K. International Observational Survey of the Effectiveness of Personal Protective Equipment during Endoscopic Procedures Performed in Patients with COVID-19. Digestion. 102:845-853, 2021
16) Arai J, Niikura R, Hayakawa Y, Sato H, Kawahara T, Honda T, Hasatani K, Yoshida N, Nishida T, Sumiyoshi T, Kiyotoki S, Ikeya T, Arai M, Suzuki N, Tsuji Y, Yamada A, Koike K. Nonsteroidal anti-inflammatory drugs prevent gastric cancer associated with the use of proton pump inhibitors after Helicobacter pylori eradication. JGH Open. 5:770-777, 2021
17) Taira N, Sawaki M, Uemura Y, Saito T, Baba S, Kobayashi K, Kawashima H, Tsuneizumi M, Sagawa N, Bando H, Takahashi M, Yamaguchi M,

Takashima T, Nakayama T, Kashiwaba M, Mizuno T, Yamamoto Y, Iwata H, Ohashi Y, Mukai H, Kawahara T, RESPECT Study Group. Health-Related Quality of Life With Trastuzumab Monotherapy Versus Trastuzumab Plus Standard Chemotherapy as Adjuvant Therapy in Older Patients With HER2-Positive Breast Cancer. J Clin Oncol. 39:2452-2462, 2021

18) Hagiwara Y, Sawaki M, Uemura Y, Kawahara T, Shimozuma K, Ohashi Y, Takahashi M, Saito T, Baba S, Kobayashi K, Mukai H, Taira N. Impact of chemotherapy on cognitive functioning in older patients with HER2-positive breast cancer: a sub-study in the RESPECT trial. Breast Cancer Res Treat. 188:675-683, 2021
19) Shiba K, Kawahara T.Using Propensity Scores for Causal Inference: Pitfalls and Tips. J Epidemiol. 31:457-463, 2021
20) Kurokawa R, Inui S, Gonoi W, Nakai Y, Ishida M, Watanabe Y, Kubo T, Amano Y, Okamoto K, Kage H, Harada S, Tanaka G, Kawahara T, Nagase T, Moriya K, Abe O. Standardized reporting systems of chest computed tomography in a population with low coronavirus disease 2019 prevalence: A retrospective comparative study. Heliyon. 7:e07743, 2021
21) Fujimoto C, Kinoshita M, Ichijo K, Oka M, Kamogashira T, Sugasawa K, Kawahara T, Yamasoba T, Iwasaki S. Cervical Vestibular Evoked Myogenic Potentials That Are Absent at 500 Hz But Present at 1000 Hz Are Characteristic of Endolymphatic Hydrops-Related Disease. Ear Hear. 42:1306-1312, 2021
22) Shiba K, Kawahara T, Aida J, Kondo K, Kondo N, James P, Arcaya M, Kawachi I. Causal Inference in Studying the Long-Term Health Effects of Disasters: Challenges and Potential Solutions. Am J Epidemiol. 190:1867-1881, 2021
23) Mukai H, Uemura Y, Akabane H, Watanabe T, Park Y, Takahashi M, Sagara Y, Nishimura R, Takashima T, Fujisawa T, Hozumi Y, Kawahara T.Anthracycline-containing regimens or taxane versus S-1 as first-line chemotherapy for meta-static breast cancer. Br J Cancer. 125:1217-1225, 2021
24) Nakayama A, Morita H, Kawahara T, Itoh H, Komuro I. Association between testosterone and lipid profiles under statin therapy and its clinical impact on the cardiovascular event risk. Heart Vessels. 36:1794-1803, 2021
25) Ohta, M. Causality assessment between reported fatal cerebral haemorrhage and suspected drugs: developing a new algorithm based on the analysis of the Japanese Adverse Event Report (JADER) database and literature review. European Journal of Clinical Pharmacology. 77: 1443-1452, 2021
26) Kadowaki H, Ishida J, Akazawa H, Yagi H, Saga-Kamo A, Umei M, Matsuoka R, Liu Q, Matsunaga H, Maki H, Sato Y, Kume H, Komuro I. Axitinib Induces and Aggravates Hypertension Regardless of Prior Treatment With Tyrosine Kinase Inhibitors. Circ Rep. 3:234-240, 2021
27) Katsushika S, Kodera S, Nakamoto M, Ninomiya K, Kakuda N, Shinohara H, Matsuoka R, Ieki H, Uehara M, Higashikuni Y, Nakanishi K, Nakao T, Takeda N, Fujiu K, Daimon M, Ando J, Akazawa H, Morita H, Komuro I. Deep Learning Algorithm to Detect Cardiac Sarcoidosis From Echocardiographic Movies. Circ J. 86:87-95, 2021
28) Katsushika S, Kodera S, Nakamoto M, Ninomiya K, Inoue S, Sawano S, Kakuda N, Takiguchi H, Shinohara H, Matsuoka R, Ieki H, Higashikuni Y, Nakanishi K, Nakao T, Seki T, Takeda N, Fujiu K, Daimon M, Akazawa H, Morita H, Komuro I. The Effectiveness of a Deep Learning Model to Detect Left Ventricular Systolic Dysfunction from Electrocardiograms. Int Heart J. 62:1332-1341, 2021
29) Umei M, Akazawa H, Saga-Kamo A, Yagi H, Liu Q, Matsuoka R, Kadowaki H, Shindo A, Nakashima A, Yasuda K, Suzuki K, Komuro I. Oral Administration of Euglena Gracilis Z Alleviates Constipation and Cardiac Dysfunction in a Mouse Model of Isoproterenol-Induced Heart Failure. Circ Rep. 4:83-91, 2021

Division of Tissue Engineering

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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 m^2 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 and Department of Eat-loss Medicine. 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 Nephrol- ogy 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.

Research activities

As for 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 addition, for the realization of bone regeneration, we are trying to apply a nanosheet which can induce osteogenesis. Now we are testing its effectiveness in large animals.

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.

In the department of tissue stem cells/ life dental science, we are doing research about engineered airway, dental pulp stem cells and umbilical cord stem cells. In addition, we investigate the mechanism of the self-generation by the tissue encapsulating the mold (BIO-TUBE).

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.

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, a clinical study of treatment for temporomandibular joint disorder taking advantage of anti-inflammatory and tissue repairing abilities of adipose stem cells has been also approved.

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, a cell analyzer and a cell sorter to the Hospital staff, letting them use with cost sharing. Various departments are conducting research using this facility.

References

1. Histochemical and Morphometrical Analyses of Scarless Wound Healing in Mouse Fetal Model. Kawakami H, Nishizawa S, Hikita A, Hoshi K. Tokai J Exp Clin Med. 2021 Apr 20;46(1):33-43.
2. Different phenotypes and chondrogenic responses of human menstrual blood and bone marrow mesenchymal stem cells to activin A and TGF-β3. Uzieliene I, Bagdonas E, Hoshi K, Sakamoto T, Hikita A, Tachtamisevaite Z, Rakauskiene G, Kvederas G, Mobasheri A, Bernotiene E. Stem Cell Res Ther. 2021 Apr 29;12(1):251.
3. Mesenchymal stromal cells in the bone marrow niche consist of multi-populations with distinct transcriptional and epigenetic properties. Kanazawa S, Okada H, Hojo H, Ohba S, Iwata J, Komura M, Hikita A, Hoshi K. Sci Rep. 2021 Aug 4;11(1):15811.
4. M1-like macrophage contributes to chondrogenesis in vitro. Miyamoto Y, Kubota K, Asawa Y, Hoshi K, Hikita A. Sci Rep. 2021 Oct 29;11(1):21307.
5. Requirement of direct contact between chondrocytes and macrophages for the maturation of regenerative cartilage. Kanda K, Asawa Y, Inaki R, Fujihara Y, Hoshi K, Hikita A. Sci Rep. 2021 Nov 18;11(1): 22476.
6. A new method of primary engineering of esophagus using orthotopic in-body tissue architecture. Suzuki K, Komura M, Obana K, Komura H, Inaki R, Fujishiro J, Suzuki K, Nakayama Y. J Pediatr Surg. 2021 Jul;56(7): 1186-1191.
7. Significant cases of central cusps, enamel pits, and oral fibromas in tuberous sclerosis complex. Taga T, Yonenaga K, Eno Y, Yasumitsu T, Hatano T, Matsuo A, Takato T. Odontology. 109(1) 279 - 283 2021
8. Association between the Mallampati score and maximal mouth opening in patients with obstructive sleep apnea. Yonenaga K, Taga H, Eno Y, Watanabe M, Matsuo A, Itai S, Ono S, Takato T. Oral Science International 18(2) 116-119 2021
9. A comparative randomized, open-label, multi-center study of the efficacy and safety of miconazole mucoadhesive tablets and miconazole gel in the treatment of Oropharyngeal Candidiasis [Translated article]. Tsuyoshi Takato, Yoshimasa Kitagawa, Yoshiaki Kamikawa, Hiromitsu Kishimoto, Seiji Nakamura, Takahide Komori, Daichi Chikatsu, Yoshiyuki Mori, Hideki Tanzawa, Akira Katakura, Akihiro Kanekawa, Masahiro Umeda, Akinori Gomi, Kazumichi Yonenaga. Medical Mycology Journal 62(1) 11 - 19 2021
10. Swallowing evaluation by the Kuchikara Taberu Balance Chart and videoendscopic examination

reveals that respiratory conditions, chewing, and position are strongly related to dysphagia. Tonosaki K, Yonenaga K, Ono S, Itai S, Oyama S, Mizuno T, Watanabe R, Hoshi K Odontology 109(2) 448-454 2021

11. Transcription Factor Hematopoietically Expressed Homeobox Protein (Hhex) Negatively Regulates Osteoclast Differentiation by Controlling Cyclin-Dependent Kinase Inhibitors. Watanabe H, Okada H, Hirose J, Omata Y, Matsumoto T, Matsumoto M, Nakamura M, Saito T, Miyamoto T, Tanaka S. JBMR Plus. 2022 Feb 14;6(4):e10608.
12. Inflammatory Arthritis and Bone Metabolism Regulated by Type 2 Innate and Adaptive Immunity. Omata Y, Frech M, Saito T, Schett G, Zaiss MM, Tanaka S. Int J Mol Sci. 2022 Jan 20; 23(3):1104.
13. Btn2a2 Regulates ILC2-T Cell Cross Talk in Type 2 Immune Responses. Frech M, Omata Y, Schmalzl A, Wirtz S, Taher L, Schett G, Zaiss MM, Sarter K. Front Immunol. 2022 Jan 25;13:757436.
14. Regulation of osteoarthritis development by ADAM17/Tace in articular cartilage. Kaneko T, Horiuchi K, Chijimatsu R, Mori D, Nagata K, Omata Y, Yano F, Inui H, Moro T, Tanaka S, Saito T. J Bone Miner Metab. 2022 Mar;40(2):196-207.
15. Lubricin Contributes to Homeostasis of Articular Cartilage by Modulating Differentiation of Superficial Zone Cells. Maenohara Y, Chijimatsu R, Tachibana N, Uehara K, Xuan F, Mori D, Murahashi Y, Nakamoto H, Oichi T, Chang SH, Matsumoto T, Omata Y, Yano F, Tanaka S, Saito T. J Bone Miner Res. 2021 Apr;36(4):792-802.
16. Involvement of Transient Receptor Potential Vanilloid Channel 2 in the Induction of Lubricin and Suppression of Ectopic Endochondral Ossification in Mouse Articular Cartilage. Nakamoto H, Katanosaka Y, Chijimatsu R, Mori D, Xuan F, Yano F, Omata Y, Maenohara Y, Murahashi Y, Kawaguchi K, Yamagami R, Inui H, Taketomi S, Taniguchi Y, Kanagawa M, Naruse K, Tanaka S, Saito T. Arthritis Rheumatol. 2021 Aug; 73(8):1441-1450.

【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

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 Co-operative 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 554.4m^2 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
Mitsuishi 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
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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.

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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, Murono 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 East Asian individuals, our team carried out a meta-analysis of GWAS data from over 400,000 individuals. We identified 61 loci that are newly implicated in predisposition to type 2 diabetes. (Nature 582, 240-245, 2020).

In collaboration with the Osaka University, RIKEN and BioBank Japan, we have identified genetic variations conferring susceptibility to deep-phenotype (diseases, biomarkers and medication usage). To expand an atlas of genetic associations in non-European populations, we conducted 220 deep-phenotype genome-wide association studies in BioBank Japan, by incorporating past medical history and text-mining of electronic medical records (Nature Genetics, 53, 1415-1424, 2021). Meta-analyses with the UK Biobank and FinnGen identified new loci, which improved the resolution of the genomic map of human traits. We performed statistical decomposition of matrices of phenome-wide summary statistics and identified latent genetic components.

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 (Nature Genetics, 5, 560-572, 2021). 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. 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 data with researchers about type 2 diabetes association study, Set3 (121,950 controls, 18,688 cases) and Set4 (7,065 controls, 2,483 cases) through national bioscience database center, NBDC (https://humandbs.biosciencedbc.jp/hum0014-v18#diabet3).

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 and revealed the genetic diagnosis on extreme phenotypes of diseases related to life-styles including, maturity onset diabetes of the young and lipodystrophy and predicted the prognosis and selected effective therapies.

3. References

1. Sakaue S, Kanai M, Tanigawa Y, Karjalainen J, Kurki M, Koshiba S, Narita A, Konuma T, Yamamoto K, Akiyama M, Ishigaki K, Suzuki A, Suzuki K, Obara W, Yamaji K, Takahashi K, Asai S, Takahashi Y, Suzuki T, Shinozaki N, Yamaguchi H, Minami S, Murayama S, Yoshimori K, Nagayama S, Obata D, Higashiyama M, Masumoto A, Koretsune Y; FinnGen, Ito K, Terao C, Yamauchi T, Komuro I, Kadowaki T, Tamiya G, Yamamoto M, Nakamura Y, Kubo M, Murakami Y, Yamamoto K, Kamatani Y, Palotie A, Rivas MA, Daly MJ, Matsuda K, Okada Y. A cross-population atlas of genetic associations for 220 human phenotypes. Nat Genet. 2021 Oct;53(10):1415-1424. doi: 10.1038/s41588-021-00931-x. Epub 2021 Sep 30. PMID: 34594039.
2. Sone K, Toyohara Y, Taguchi A, Miyamoto Y, Tanikawa M, Uchino-Mori M, Iriyama T, Tsuruga T, Osuga Y. Application of artificial intelligence in gynecologic malignancies: A review. J Obstet Gynaecol Res. 2021, Aug;47(8): 2577-2585. doi: 10.1111/jog.14818. Epub 2021 May 10. PMID: 33973305.
3. Hosoe J, Kawashima-Sonoyama Y, Miya F, Kadowaki H, Suzuki K, Kato T, Matsuzawa F, Aikawa SI, Okada Y, Tsunoda T, Hanaki K, Kanzaki S, Shojima N, Yamauchi T, Kadowaki T. Genotype-Structure-Phenotype Correlations of Disease-Associated IGF1R Variants and Similarities to Those of INSR Variants. Diabetes. 2021 Aug;70(8):1874-1884. doi: 10.2337/db20-1145. Epub 2021 Jun 1. PMID: 34074726.
4. Hosoe J, Suzuki K, Miya F, Kato T, Tsunoda T, Okada Y, Horikoshi M, Shojima N, Yamauchi T, Kadowaki T. Structural basis of ethnic-specific variants of PAX4 associated with type 2 diabetes. Hum Genome Var. 2021 Jul 5;8(1):25. doi: 10.1038/s41439-021-00156-8. PMID: 34226521; PMCID: PMC8257626.

5. Imamura M, Takahashi A, Matsunami M, Horikoshi M, Iwata M, Araki SI, Toyoda M, Susarla G, Ahn J, Park KH, Kong J, Moon S, Sobrin L; International Diabetic Retinopathy and Genetics CONsortium (iDRAGON), Yamauchi T, Tobe K, Maegawa H, Kadowaki T, Maeda S. Genome-wide association studies identify two novel loci conferring susceptibility to diabetic retinopathy in Japanese patients with type 2 diabetes. Hum Mol Genet. 2021 May 17;30(8): 716-726. doi: 10.1093/hmg/ddab044. Erratum in: Hum Mol Genet. 2022 Jul 7;31(13):2294. PMID: 33607655; PMCID: PMC9022108.
6. Mahajan A, Spracklen CN, Zhang W, Ng MCY, Petty LE, Kitajima H, Yu GZ, Rüeger S, Speidel L, Kim YJ, Horikoshi M, Mercader JM, Taliun D, Moon S, Kwak SH, Robertson NR, Rayner NW, Loh M, Kim BJ, Chiou J, Miguel-Escalada I, Della Briotta Parolo P, Lin K, Bragg F, Preuss MH, Takeuchi F, et al. Multi-ancestry genetic study of type 2 diabetes highlights the power of diverse populations for discovery and translation. Nat Genet. 2022 May;54(5):560-572. doi: 10.1038/s41588-022-01058-3. Epub 2022 May 12. PMID: 35551307; PMCID: PMC9179018.

Advanced Medical Center for Heart Failure

Director, Associate Professor
Masaru Hatano, M.D.,Ph.D.

Vice Director
Masahiko Ando, M.D., Ph.D.

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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.

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 186
  Heart tansplantation to date (as of 31 Aug 2022), 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 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.

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, Maemura S, Suzuki T, Takiguchi H,

Kubota Y, Seo K, Sakata A, Nomura S, Hatano M, Ueda K, Harada M, Toko H, Takimoto E, Akazawa H, Nishimura S, Komuro I . Three-Dimensional Visualization of Hypoxia-Induced Pulmonary Vascular Remodeling in Mice.. Circulation. 2021; 144(17):1452-1455.

2. Ide T, Kaku H, Matsushima S, Tohyama T, Enzan N, Funakoshi K, Sumita Y, Nakai M, Nishimura K, Miyamoto Y, Tsuchihashi-Makaya M, Hatano M, Komuro I, Tsutsui H; JROADHF Investigators. Clinical Characteristics and Outcomes of Hospitalized Patients With Heart Failure From the Large-Scale Japanese Registry Of Acute Decompensated Heart Failure (JROADHF). Circ J. 2021;85(9):1438-1450.
3. Kaneko H, Kiriyama H, Kamon T, Itoh H, Kodera S, Fujiu K, Daimon M, Morita H, Hatano M, Komuro I. Percutaneous Mitral Valve Intervention Using MitraClip for Functional Mitral Regurgitation and Heart Failure. Int Heart J. 2021; 62(1):4-8.
4. Bujo C, Amiya E, Hatano M, Tsuji M, Maki H, Ishida J, Ishii S, Narita K, Endo M, Ando M, Shimada S, Kinoshita O, Ono M, Komuro I. Association between infectious event and de novo malignancy after heart transplantation. Heart Vessels. 2021;36(4):499-508.
5. Ishiwata J, Daimon M, Nakanishi K, Sugimoto T, Kawata T, Shinozaki T, Nakao T, Hirokawa M, Sawada N, Yoshida Y, Amiya E, Hatano M, Morita H, Yatomi Y, Komuro I. Combined evaluation of right ventricular function using echocardiography in non-ischaemic dilated cardiomyopathy. ESC Heart Fail. 2021 ;8(5):3947-3956.
6. Bujo C, Amiya E, Hatano M, Ishida J, Tsuji M, Kakuda N, Narita K, Saito A, Yagi H, Ando M, Shimada S, Kimura M, Kinoshita O, Ono M, Komuro I. Long-Term renal function after implantation of continuous-flow left ventricular assist devices: A single center study. Int J Cardiol Heart Vasc. 2021;37:100907.
7. Tsuji M, Amiya E, Bujo C, Hara T, Saito A, Minatsuki S, Maki H, Ishida J, Hosoya Y, Hatano M, Imai H, Nemoto M, Kagami Y, Endo M, Kimura M, Ando M, Shimada S, Kinoshita O, Ono M, Komuro I. Carbon Monoxide Diffusing Capacity Predicts Cardiac Readmission in Patients Undergoing Left Ventricular Assist Device Implantation in Japan. ASAIO J. 2021;67(10): 1111-1118.
8. Goto K, Uehara M, Okamoto K, Takeda N, Morita H, Hatano M, Komuro I. The therapeutic dilemma of immunosuppressive drugs for refractory cardiac sarcoidosis in COVID-19 infection. ESC Heart Fail. 2021;8(6):5577-5582.
9. Minatsuki S, Kiyosue A, Shimizu Y, Tanikawa I, Murasawa T, Hirose K, Saito A, Yagi H, Takeda N, Hatano M, Ando J, Komuro I. A Novel Technique of Balloon Pulmonary Angioplasty for the Treatment of Total Occlusion Lesions. CJC Open. 2021;3(12):1513-1515.
10. Tamura Y, Kumamaru H, Abe K, Satoh T, Miyata H, Ogawa A, Tanabe N, Hatano M, Yao A, Tsujino I, Fukuda K, Kimura H, Kuwana M, Matsubara H, Tatsumi K; Japan Pulmonary Hypertension Registry (JAPHR) Network. Improvements in French risk stratification score were correlated with reductions in mean pulmonary artery pressure in pulmonary arterial hypertension: a subanalysis of the Japan Pulmonary Hypertension Registry (JAPHR). BMC Pulm Med. 2021;21(1): 28.
11. Dai Z, Uehara M, Amiya E, Hatano M, Komuro I. Acute cellular rejection after heart transplantation and its remission visualized by cardiac magnetic resonance. Eur Heart J Case Rep. 2021;5(3): ytab085.
12. Ikawa T, Miyagawa T, Fukui Y, Minatsuki S, Maki H, Inaba T, Hatano M, Toyama S, Omatsu J, Awaji K, Norimatsu Y, Watanabe Y, Yoshizaki A, Sato S, Asano Y. Association of serum CCL20 levels with pulmonary vascular involvement and primary biliary cholangitis in patients with systemic sclerosis. Int J Rheum Dis. 2021;24(5):711-718.
13. Adachi Y, Kiyosue A, Ando J, Kawahara T, Kodera S, Minatsuki S, Kikuchi H, Inaba T, Kiriyama H, Hirose K, Shinohara H, Saito A, Fujiwara T, Hara H, Ueda K, Sakakura K, Hatano M, Harada M, Takimoto E, Akazawa H, Morita H, Momomura SI, Fujita H, Komuro I. Factors associated with left ventricular reverse remodelling after percutaneous coronary intervention in patients with left ventricular systolic dysfunction. Sci Rep. 2021;11(1):239.

14. Minatsuki S, Takahara M, Kiyosue A, Kodera S, Hatano M, Ando J, Kohsaka S, Ishii H, Shinke T, Amano T, Ikari Y, Komuro I; J-SHD and J-PCI Investigators. Characteristics and in-hospital outcomes of patients undergoing balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension: a time-trend analysis from the Japanese nationwide registry. Open Heart. 2021;8(2):e001721.
15. Kakuda N, Amiya E, Hatano M, Maki H, Bujo C, Tsuji M, Narita K, Fujita K, Ishida J, Ono M, Komuro I. Case Report: A Case of Acute Cellular Rejection Due to Atopic Dermatitis Exacerbation 3 Years After Heart Transplantation. Front Immunol. 2021;12:630051.
16. Kadowaki H, Ishida J, Uehara M, Ishizuka M, Kiyosue A, Hatano M, Shimada S, Ono M, Akazawa H, Komuro I. Detection of Profound Myocardial Damage by Cardiac MRI in a Patient with Severe Cardiotoxicity Induced by Anti-HER2 Therapy. Int Heart J. 2021;62(6):1436-1441.
17. Yasunaga M, Yasuda Y, Honda A, Maki H, Toyama K, Masamoto Y, Bujo C, Amiya E, Hatano M, Ono M, Komuro I, Kurokawa M.Successful treatment of EBV-related lymphoproliferative disease after heart transplantation with autologous hematopoietic stem cell transplantation despite transient heart failure associated with engraftment syndrome. Ann Hematol. 2021 ;100(4):1097-1100.
18. 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. Cardiol. 2022;80(2):110-115.

Swallowing Center

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Introduction and Organization

A condition in which there is a problem with swallowing food or drink is called a swallowing disorder. In recent years, advances in medical technology have increased the lifesaving rate and the 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 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 mornings. 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 various cases with a multidisciplinary team.

We also actively perform surgical treatment for dysphagia (to prevent aspiration or to improve swallowing functions) and provides intensive rehabilitation after surgery to improve swallowing functions during hospitalization.

The following is a list of swallowing examinations performed in 2021.

- Videofluorographic swallowing study: 637 cases
- Videoendoscopic examination of swallowing: 575 cases
- High-resolution swallowing manometry: 45 cases

- Swallowing computed tomography: 9 cases

Teaching activities

The center emphasizes educational activities on feeding and swallowing throughout the hospital and actively organizes E-learning and training sessions.

We participate in undergraduate education as a part of systemic lectures and bedside learning by the department of Otolaryngology and Head and Neck Surgery and Rehabilitation Medicine.

Research activities

Our research field covers a variety of topics related to swallowing. Clinical and basic research activities are highly encouraged. The clinical research is related to swallowing dynamics and physiology, laryngology, broncho-esophagology and rhinology and is related to case research, and clinical statistics.

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. Effects of aspiration prevention surgery on patients with severe dysphagia
2. Pulmonary inflammatory responses by contrast agent aspiration
3. Swallowing mechanisms using pathological and electrophysiological analysis and VR system
4. Esophageal Motility in Neuromuscular Disorders
5. Evaluation of swallowing physiology with pharyngo-esophageal high-resolution manometry
6. Regeneration of vocal fold structure and its molecular mechanism
7. Gene expression analysis of recurrent respiratory papillomatosis
8. Pathophysiology of olfactory dysfunction due to COVID-19
9. Research on preventive rehabilitation for dysphagia due to chemoradiotherapy for head and neck cancer
10. Pathophysiology of dysphagia after esophageal cancer surgery
11. Statistical analysis of dysphagia patients using big data
12. Research on the effect of cervical spine surgery on swallowing function

References

1. Kataoka T, Yoshida S, Ueha R. Clicking Sensation on Swallowing. Jama Otolaryngol. 147(8):762-3. 2021.
2. Koyama S, Kondo K, Ueha R, Kashiwadani H, Heinbockel T. Possible Use of Phytochemicals for Recovery from COVID-19-Induced Anosmia and Ageusia. International journal of molecular sciences. 22(16). 2021.
3. Koyama S, Ueha R, Kondo K. Loss of Smell and Taste in Patients With Suspected COVID-19: Analyses of Patients' Reports on Social Media. J Med Internet Res. 23(4). 2021.
4. Masuda H, Ueha R, Sato T, Goto T, Koyama M, Yamauchi A, Kaneoka A, Suzuki S, Yamasoba T. Risk Factors for Aspiration Pneumonia After Receiving Liquid-Thickening Recommendations. Otolaryngology--head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery. doi: 10.1177/01945998211049114. 2021.
5. Mori E, Ueha R, Kondo K, Funada S, Shimmura H, Kanemoto K, Tanaka H, Nishijima H, Otori N, Yamasoba T, Kojima H. Squamous and Respiratory Metaplasia After Olfactory Mucosal Resection. Front Neurosci. 15:695653. 2021.
6. Nativ-Zeltzer N, Ueha R, Nachalon Y, Ma B, Pastenkos G, Swackhamer C, Bornhorst GM, Lefton-Greif MA, Anderson JD, Belafsky PC. Inflammatory Effects of Thickened Water on the Lungs in a Murine Model of Recurrent Aspiration. Laryngoscope. 131(6):1223-8. 2021.
7. Sato T, Ueha R, Goto T, Yamauchi A, Kondo K, Yamasoba T. Expression of ACE2 and TMPRSS2 Proteins in the Upper and Lower Aerodigestive Tracts of Rats: Implications on COVID 19 Infections. Laryngoscope. 131(3):E932-E9. 2021.
8. Sekiguchi Koyama M, Ueha R, Goto T, Sato T, Tachibana A, Mizumoto Y, Nito T, Yamasoba T. Aspiration Prevention Surgery under Local Anesthesia for Palliative Care in Patients with Head and Neck Cancer: A Report of Two Cases. ORL J Otorhinolaryngol Relat Spec. 83(1):52-8. 2021.
9. Sugaya T, Ueha R, Sato T, Goto T, Yamauchi A, Yamasoba T. Safety of surgical tracheostomy

under continued antithrombotic therapy: A retrospective cohort study. Clinical otolaryngology. doi: 10.1111/coa.13861. 2021.

10. Takeuchi M, Ahn J, Lee K, Takaki K, Ifukube T, Yabu K, Ueha R, Sekino M. Hands-free wearable electrolarynx using LPC residual waves and listening evaluation by laryngectomies. Advanced Biomedical Engineering. 11:68-75, 2021.
11. Ueha R, Kondo K, Kagoya R, Shichino S, Shichino S, Yamasoba T. ACE2, TMPRSS2, and Furin expression in the nose and olfactory bulb in mice and humans. Rhinology. 59(1):105-9. 2021
12. Ueha R, Sato T, Goto T, Koyama M, Yamauchi A, Mizukami A, Yamasoba T. Effects of Aspiration Prevention Surgery on the Dynamics of the Pharynx and Upper Esophageal Sphincter. OTO Open. 5(4):2473974X211048505. 2021
13. Ueha R, Sato T, Goto T, Yamauchi A, Nativ-Zeltzer N, Mitsui J, Belafsky PC, Yamasoba T. Esophageal Dysmotility is Common in Patients With Multiple System Atrophy. Laryngoscope. 131(4):832-8. 2021
14. Uranaka T, Kashio A, Ueha R, Sato T, Bing H, Ying G, Kinoshita M, Kondo K, Yamasoba T. Expression of ACE2, TMPRSS2, and Furin in Mouse Ear Tissue, and the Implications for SARS-CoV-2 Infection. Laryngoscope. 131(6):E2013-E7. 2021.

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 8 TNF inhibitors, 3 IL-6 inhibitors, 1 CTLA4-Ig, 4 IL-17 inhibitors, 1 IL-12/23 inhibitor, 2 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 typeI IFN inhibitor, 2 complement activation inhibitors, 1 nFcR inhibitor, and 5 JAK inhibitors and 1 PDE4 inhibito have been approved "small-molecule inhibitorss". 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 1,300 in 2021, with 65% subcutaneous, 30% intravenous, and 5% 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. Shimizu T, Nagafuchi Y, Harada H, Tsuchida Y, Tsuchiya H, Hanata N, Tateishi S, Kanda H, Sumitomo S, Soda H, Yamamoto K, Fujio K. Decrease peripheral blood memory B cells are associated with the presence of interstitial lung disease in rheumatoid arthritis: a case-control study. Mod Rheumatol. 2021; 31: 127-32
2. Kanda H. Evaluation of activity for Psoriatic arthritis. Nippon Rinsho. 2021; 79: 534-539
3. Kanda H. Safety of tofacitinib for rheumatoid arthritis. Rheumatology. 2021; 65: 494-501
4. Kanda H. Cyclosporin in lupus nephritis. Kidney and dialysis. 2021; 91: 143-6
5. Kanda H. IgA vasculitis. Kidney and dialysis. 2021; 91: 143-6
6. Kanda H. Methotrexate in psoriatic arthritis. Diagnosis and treatment. 2021; 109: 1641-5

Medical Community Network and Discharge Planning Center

Associate Professor

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Assistant Profeesor

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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 9 medica I 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 spedalized 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 Janualy 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.

Department of Cancer Resource Center

Chief

Sachiyo Nomura, M.D.,Ph.D.

Associate chief

Takako Wakeda, M.D., Ph.D.

Counseling staff

Yuko Irisawa, RN., Keiko Fukuda, RN., Kunie Wakao, RN.

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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.

Center for Disease Biology and Integrative Medicine

Laboratory of Molecular Biomedicine for Pathogenesis

Professor

Toru Miyazaki, M.D., Ph.D.

Associate Professor

Satoko Arai, Ph.D.

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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 definitively 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 blood-stream, 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. Hasegawa H, Mizoguchi I, Orii N, Inoue S, Katahira Y, Yoneto T, Xu M, Miyazaki T & Yoshimoto T. IL-23p19 and CD5 antigen-like form a possible novel heterodimeric cytokine and contribute to experimental autoimmune encephalomyelitis development. Sci. Rep. 11, 5266 (2021).
2. Lee J Y, Arumugarajah S, Lian D, Maehara N, Haig A R, Suri R S, Miyazaki T, & Gunaratna L. Recombinant Apoptosis Inhibitor of Macrophage Protein Reduces Delayed Graft Function in a Murine Model of Kidney Transplantation. PloS One. 16, e0249838 (2021).
3. Maehara N, Taniguchi K, Okuno A, Ando H, Hirota A, Li Z, Wang C-T, Arai S, & Miyazaki T. AIM/CD5L attenuates DAMPs in the injured brain and thereby ameliorates ischemic stroke. Cell Rep. 36, 109693 (2021).
4. Wang C-T, Tezuka T, Takeda N, Araki K, Arai S, & Miyazaki T. High salt exacerbates acute kidney injury by disturbing the activation of CD5L/ apoptosis inhibitor of macrophage (AIM) protein. PloS One. 16, e0260449 (2021).

Laboratory of Structural Physiology

Professor

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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.

The 17 members of our laboratories in the April of 2021 are Haruo Kasai, Sho Yagishita (Lecturer), Yusuke Iino (Resaerch Associate), Takeshi Sawada (Resaerch Associate), Hasan Ucar (Project Researcher), Mio Tajiri (Project Researcher), Yuichi Morimoto (Project Researcher), Toshiaki Kume (D4), Hitoshi Okazaki (D2), Hidefumi Ohmi (M2), and as technical staffs, Arisa Kurabayashi, Shizuka Fujii, Yuki Sakata, Masayoshi Asaumi, Chie Fujinami, Akiko Abe and Yumiko Saikachi.

Teaching activities

We gave three lectures of physiology for undergraduate students, was responsible for one student experiment, four lectures of physiology and neuroscience for master course students, organized ten lectures of the functional biology for graduate students. The final lecture of Haruo Kasai was held on March 3, 2022 for his retirement from Medical School. One undergraduate student joined the activity of our laboratory for free quarter (FQ).

Research activities

Functional imaging is a central theme in modern biology and medicine. All biological functions involve a multitude of interactions at the molecular, cellular, and system levels, and it is ultimately desirable to perform molecular and cellular imaging in intact preparations in which the original in vivo functions are preserved. We have been exploring two-photon excitation microscopy with a new type of laser, an infrared femtosecond-pulse laser, as a means to achieve this goal. The two-photon microscope has the ability to penetrate deep into tissues and is the only imaging instrument that allows investigations of intact tissues at the cellular and molecular levels. Two-photon microscopy can also be readily combined with molecular biological and other physiological methods, and it promises to provide important insight into

various biological processes in the coming years. Our research interests have two main focuses: (1) the dynamics of synapses in the cerebral cortex and (2) exocytosis in both neurons and secretory cells. We welcome multidisciplinary collaborations to promote our research goals and to help to adapt the new microscopic techniques and lasers to a wide range of biomedical applications.

(1) Dendritic spines

Dendritic spines are postsynaptic to most excitatory synapses in the brain, and their structural changes are a major cellular basis for learning and memory (Kasai, et al. 2010. Spine generation and elimination are robust processes, even in the adult brain, and spine enlargement and shrinkage play key roles in the plasticity of dendritic spines. We previously used two-photon glutamate uncaging to stimulate individual spines and demonstrated that dendritic spine enlargement underlay long-term potentiation (LTP) at the level of single spines (Matsuzaki, Nature 2004). We also reported that spine shrinkage and elimination can be induced when glutamate uncaging was paired with action potentials in the presence of GABAergic inhibition (Hayama, 2013). Spine structures are dynamically maintained by the regulation of actin fibers (F-actins). Cofilin is a highly abundant actin-regulatory protein, which binds to and alters the physical properties of F-actin. Dephosphorylated cofilin at its serine-3 residue (dp-cofilin) cleaves F-actin to generate new barbed ends that are sites for actin polymerization and depolymerizes F-actin at its pointed end to reduce fiber length. These bidirectional enzymatic activities of cofilin are inhibited by its phosphorylation at the serine-3 residue, as phosphorylated cofilin (p-cofilin) dissociates from F-actin. Thus, the entire lifecycle of F-actin is regulated by cofilin. Dendritic spine enlargement and shrinkage are likely also regulated by the phosphorylation and dephosphorylation of cofilin1 (Noguchi, 2016). We previously showed that bidirectional structural plasticity is controllable in individual spines by modulating cofilin phosphorylation (Hayama,, Kasai, Nat, Neurosci. 2013). We have also made a optic probe which labels enlarged spines, and optically erase them after learning, and first demonstrated the causal relationship between spine enlargement and memory (Hayashi, 2015).

In this year, we have explored dopamine actions on spine dynamics and pyschosis. Psychosis is a debilitating psychological condition with a long history. Described in the medical writings of Hippocrates as early as the 4th century B.C., the psychotic state of hallucinations, delusions and disordered thought represent an existential threat to an afflicted human mind. Now, a team of researchers from the International Research Center for Neurointelligence (IRCN) and the Graduate School of Medicine at the University of Tokyo, and the Graduate School of Informatics at Kyoto University, proposes that psychosis involves defective neural signaling in a deep brain area called the ventral striatum during a behavior called discrimination learning (Ref. 1).

We studied the way mice predict future rewards in their environment, a behavior known as reward learning, which is shared by us humans and other mammals, too. Reward learning involves the release of a chemical messenger dopamine to a receptor protein in the brain called dopamine D1 receptor (D1R) to signal the anticipation of a reward. Specifically, the team searched for a second dopamine signal that occurs only when the anticipated reward fails to materialize — reward omission.

We suspected this signal for reward omission existed in neurons of the ventral striatum area of the brain that contain a counterpart to D1R, dopamine D2 receptor (D2R). Coincidentally, D2R is the major brain receptor for nearly every antipsychotic medication used to date. The team showed that reward omission triggers a signal in these neurons called the dopamine dip, a drop in dopamine levels, which lasts less than a second.

These dips seem to contribute to the process of discrimination learning, which includes how all animals, including humans, judge previously learned rewards and punishments. To explore the connection between dips and discrimination learning, the researchers used sophisticated optogenetic technologies to artificially increase or decrease the dips for the first time and measured their effects on how the mice estimated rewards. Optogenetics is a way to activate artificial light-sensitive proteins with finely controlled laser light to turn neuronal activity on or off.

(2) Mechanical actions on presynaptic exocytosis (Ref. 8).

In the brain, synapses are often formed on small protrusions (< 1 μm) from dendrites, called dendritic spines. These spines touch small swellings called presynaptic boutons, found on neighbouring neurons, which release glutamate when they receive an action potential. In 2004, our lab discovered the rapid enlargement of spines, using a technique called repetitive two-photon uncaging[1]. Back then, it was evident that enlarged spines pressed onto the presynaptic terminals, which are tightly connected to the spines via the synaptic junction. Technical hurdles prevented further exploration of this effect until recently. Instead, we and other laboratories have focused on how enlargement affected the spines themselves[2]. Enlargement is confined to the stimulated spine and has a long-lasting component (> 2hr), which is accompanied by increases in glutamate sensitivities. This gives a cellular basis to the conceptual framework of memory and cell assembly referred to as Hebb's rule: Neurons that fire together, wire together. Now, we address the remaining questions: Is the force of spine-enlargement utilized for other purposes, and can we measure this force acting in brain tissue?

Although two-photon glutamate uncaging has enabled studies of single synapse physiology, we needed to wait for some key technical advances before using it to study presynaptic terminals. These advances were: 1) optogenetic induction of action potential in presynaptic neurons; 2) a fluorescent protein called iGluSnFR that can detect glutamate release; 3) a technique called iSLIM, to image the assembly of SNARE proteins that enable the ultrafast exocytosis of glutamate from presynaptic boutons when triggered by an action potential.

We found that spine enlargement induced by two-photon uncaging pushed the presynaptic terminal, recessed the bouton, enhanced assembly of SNARE complexes in the bouton and augmented the glutamate release caused by optogenetic induction of action potential. This new phenomenon was named PREST (PREssure Sensation and Transduction). Similar effects were seen when the presynaptic terminal was recessed by pushing it with a sharp glass electrode, or through increases in osmotic pressure. These forces on the presynaptic terminal are roughly 0.5 atm, or 0.5 kg/cm^2, comparable to the forces produced by smooth muscle contraction. This suggests that these muscle-like forces in the brain facilitate the assembly of SNAREs, and thereby lead to exocytosis. Since the spine is the most actin-rich structure in neurons, it is not surprising that a single spine is capable of producing an estimated 10 nN of force. Unexpectedly, though, PREST continued for more than 20 min after cells regained their shape, implying that some traces of the change remain inside the cells. Spine enlargement also has a prominent rapid and transient compound (< 10 min), and it had been puzzling that this is not strongly associated with the increases in glutamate sensitivity caused by the longer-lasting component[1]. Thus, PREST may instead read out the rapid enlargement of a spine for a particular function, possibly for a working memory.

Synaptic transmission has previously been considered either chemical or electrical. Our finding indicates that synapses can be mechanical as well. Thus, the structural dynamics of synapses play major roles in the formation of networks over a time scale less than 10 s. PREST is a novel notion in the field of mechanobiology, and since SNARE proteins are ubiquitous it may operate in many cell types.

The force of spine enlargement is utilized in two different ways: it acts to expand the spine itself, and it also acts on the presynaptic terminal for a rapid readout of the postsynaptic event by PREST. Both mechanisms are still largely mysterious, and this paper reveals only the tip of the iceberg. For example, PREST also involves cellular structures in other regions, including the active zone, vesicle clusters, actin-based scaffolds and microtubules.

Discovering the underlying mechanisms behind the mechanical force and PREST — and finding ways to manipulate them — are key to understand their functions in the brain, and their roles in learning and memory. Many molecules

influencing our intelligence and mental disorders are concentrated in spine synapses, and methods to control the generation of mechanical force and PREST will help to understand many other mysteries of the brain.

References

1. Iino, Y., Sawada, T., Yamaguchi, Tajiri, M., K., Ishii, S., Kasai, H.* & Yagishita, S.* (2020) Dopamine D2 receptors in discrimination learning and spine enlargement. *Nature* 579: 555-560.
2. Seaton, G., Hodges, G., de Haan, A., Grewal, A., Pandey, A., Kasai, K. & Fox, K. (2020) Dual-component structural plasticity mediated by alphaCaMKII-autophosphorylation on basal dendrites of cortical layer 2/3 neurones. *J. Neurosci.*, 40:2228-2245.
3. Lee, S., Kume, H., Urakubo, H., Kasai, H., Ishii, S. (2020) Multi-scale U-net for Two-Photon Microscopy Image Denoising and Restoration in Neural Networks. Neural Networks 125:92-103.
4. Ishii, S., Lee, Sehyung, Urakubo, H., Kume, H., Kasai, H. (2020) Generative and discriminative model-based approaches to microscopic image restoration and segmentation. *Microscopy* 69, 79-91.
5. Fujita, Y., Yagishita, S., Kasai, H., Ishii, S. (2020) Computational Characteristics of the Striatal Dopamine System Described by Reinforcement Learning With Fast Generalization. Frontier in Computational Neuroscience, 22 July, 2020. DOI: 10.3389/fncom.2020.00066
6. Urakubo, H., Yagishita, S., Kasai, H., & Ishii, S. (2020) Signaling models for dopamine-dependent temporal contiguity in striatal synaptic plasticity. PLoS Computational Biology, July 23, 2020.
7. Hao Wang, Kouichi Mizuno, Noriko Takahashi, Eri Kobayashi, Jun Shirakawa, Yasuo Terauchi, Haruo Kasai, Katsuhide Okunishi, Tetsuro Izumi (2020) Melanophilin Accelerates Insulin Granule Fusion Without Predocking to the Plasma Membrane, Diabetes 69:2655-2666.
8. Ucar, H., Morimoto, Y., Watanabe, S., Noguchi, J., Iino, Y., Yagishita, S., Takahashi, N. & Kasai, H. (2021). Mechanical actions of dendritic-spine enlargement on presynaptic exocytosis. *Nature* 600: 686-689.
9. Kasai, H., Ziv, N. E., Okazaki, H., Yagishita, S. & Toyoizumi, T. (2021) Spine dynamics in the brain, mental disorders and artificial neural networks. *Nature Reviews Neuroscience* 22: 407-422.
10. Shimizu, G., Yoshida, K., Kasai, H. & Toyoizumi, T. (2021) Computational Roles of Intrinsic Synaptic Dynamics, *Current Opinions in Neuroscience 70:34-42.*
11. Urakubo, H., Yagishita, S., Kasai, H., Kubota, Y. & Ishii, S. (2021) Molecular concentrations required for dopamine dip-detection in D2 striatal-projection neurons. *PLoS Computational Biology* 17:e1009364.
12. Kasai, H. & Ucar, H. (2021) Forceful synapses reveal mechanical interactions in the brain. *Nature* online 24 November 2021. DOI:10.1038/d41586-021-03516-0.

Laboratory of Biomedical Equipment and Biomaterials

Professor

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Kanako Harada, Ph.D.

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Introduction and Organization

The Division tightly collaborates with Faculty of Engineering. Prof. Ito charged at Department of Chemical System Engineering and Bioengineering. Associate Professor Harada charged at Department of Mechanical Engineering and Bioengineering.

Teaching activities

Prof. Ito and Associate Prof. Harada are sharing duties for undergraduate and graduate students of both Graduate School of Medicine and Graduate School of Engineering. They give lectures on biomedical engineering at Graduate School of Medicine. Prof. Ito gives a lecture concerning biosystem engineering, separation technology I, biotechnology II, Basic Biology, and Overview of Chemical Bioengineering at the Chemical System Engineering course and Bio-engineering course at Graduate School of Engineering School. Associate Prof. Harada teaches at the courses titled Bioengineering Exercise for Social Implementation 1・2, Engineering Competency III -Summer Camp-, Engineering Competency I -PBL-, Basic Biology, Overview of Mechano Bioengineering, and Clinical Biomechanics.

Research activities

Biomaterials are one of important keys in medicine and medical engineering. In the field of tissue engineering, scaffold materials are extremely important. In the drug delivery field, drugs are encapsulated in various materials which achieve ideal release kinetics. The functions of these biomaterials and phenomena inside and outside biomaterials in vivo are complicated both in terms of chemistry and biology. Ito Laboratory is trying to design and develop novel biomaterials for tissue engineering and drug delivery by the combination of medicine and chemical system engineering. Especially we focus on hydrogels which can be utilized for islet regeneration and drug delivery in peritoneum.

1) Development of Hydrogels for medical uses
- Development of novel *in situ* crosslinked hydrogels for a medical use using hyaluronan, chitosan, dextran, alginate, gelatin, carboxymethyl cellulose and synthetic dendritic polymers.

2) Development of particles for medical uses
- Nano-sized semi-conductor and metal particles for imaging
- Micro-sized particles composed of PLGA, PEG, Albumin.

3) Challenge to establish novel treatments using new medical hydrogels and particles.
- Peritoneal adhesion prevention
- Hemostats
- Drug delivery for peritoneal dissemination, Mesothelioma, Liver cirrhosis
- Hydrogel scaffolds for regeneration of islets and bones
- Artificial Oxygen Carriers

In addition, Associate Professor Harada and his students are developing surgical skill assessment methods, surgical robots and robots assisting scientific experiments.

1. Surgical Skill Assessment

Data sets collected during simulated surgery have been analyzed to quantify surgical skills. For example, an image processing method to detect a surgical suture has been developed to be used to quantify the manipulation skills of expert surgeons.

2. Surgical robots

Surgical robotic systems for pediatric surgery, neurosurgery and eye surgery have been developed. To study automation of robotic assistance, an autonomous collision avoidance method has been developed to avoid collision between robotic tools and between a robotic tool and tissues. An autonomous tool guidance method has been developed to assist the looping task in a small body space.

3. Robots assisting scientific experiments

A robotic platform to assist scientific experiments, such as the dissection of mouse, has been designed in collaboration with mathematicians, AI researchers, robot researchers, and scientists.

References

(1) Y. Oki, K. Harano, Y. Hara, Y. Sasajima, R. Sasaki, T. Ito, M. Fujishiro, T. Ito "Cationic surface charge effect on proliferation and protein production of human dental pulp stem cells cultured on diethylaminoethyl-modified cellulose porous beads" ***Biochemical Engineering Journal***, 2021, 176, 108217

(2) K. Yamaguchi, O. Hiraike, H. Iwaki, K. Matsumiya, N. Nakamura, K. Sone, S.Ohta, Y. Osuga, T. Ito "Intraperitoneal administration of cisplatin-loaded nanogel through a hybrid system containing alginic acid-based nanogel and in situ cross-linkable hydrogel for peritoneal dissemination of ovarian cancer" ***Molecular Pharmaceutics***, 2021, 18, 4090−4098

(3) X. Fu, S. Ohta, T. Kawakatsu, M. Kamihira, Y. Sakai, T. Ito "Bioinspired perfluorocarbon-based oxygen carriers with concave shape and deformable shell" ***Advanced Materials Technologies***, 2021, 2100573

(4) A.K..S. Chandel, A. Shimizu, K. Hasegawa, T. Ito "Advancement of biomaterial-based postoperative adhesion barriers" ***Macromolecular Bioscience***, 2021, 2000395

(5) M. Okawa, M. Sakoda, S. Ohta, K. Hasegawa, Y. Yatomi, and T. Ito "The balance between the hemostatic effect and immune response of hyaluronan conjugated with different chain lengths of inorganic polyphosphate", ***Biomacromolecules***, 2020, 21(7), 2694-2704

(6) A. Huaulmé, D. Sarikaya, K. Le Mut, F. Despinoy, Y. Long, Q. Dou, CB. Chng, W. Lin, S. Kondo, L. Bravo-Sánchez, P. Arbeláez, W. Reiter, M. Mitsuishi, K. Harada, P. Jannin, “MIcro-surgical anastomose workflow recognition challenge report”, ***Comput. Methods Programs Biomed.*** 2021, 212: 106452.

(7) SA. Heredia Perez, MM. Marinho, K. Harada, M. Mitsuishi, “The effects of different levels of realism on the training of CNNs with only synthetic images for the semantic segmentation of robotic instruments in a head phantom”, ***Int J Comput Assist Radiol Surg,*** 2020, 15(8):1257-1265.

(8) MM. Marinho, H. Ishida, K. Harada, K. Deie, M. Mitsuishi, “Virtual Fixture Assistance for Suturing in Robot-Aided Pediatric Endoscopic Surgery”, ***IEEE Robot Autom Lett,*** 2020, 5.2: 524-531.

(9) A. Nakazawa, K. Harada, M. Mitsuishi, P. Jannin, “Real-time surgical needle detection using region-based convolutional neural networks”, ***Int J Comput Assist Radiol Surg,*** 2020, 15:41-47.

Laboratory of Clinical Biotechnology

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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 afore-mentioned 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). 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. Wang JS, Kamath T, Mazur CM, Mirzamohammadi F, Rotter D, Hojo H, Castro CD, Tokavanich N, Patel R, Govea N, Enishi T, Wu Y, da Silva Martins J, Bruce M, Brooks DJ, Bouxsein ML, Tokarz D, Lin CP, Abdul A, Macosko EZ, Fiscaletti M, Munns CF, Ryder P, Kost-Alimova M, Byrne P, Cimini B, Fujiwara M,

Kronenberg HM, Wein MN. Control of osteocyte dendrite formation by Sp7 and its target gene osteocrin. *Nat Commun*. 12(1):6271, 2021

2. Yamada D, Nakamura M, Takao T, Takihira S, Yoshida A, Kawai S, Miura A, Ming L, Yoshitomi H, Gozu M, Okamoto K, Hojo H, Kusaka N, Iwai R, Nakata E, Ozaki T, Toguchida J, Takarada T. Induction and expansion of human PRRX1 + limb-bud-like mesenchymal cells from pluripotent stem cells. *Nat Biomed Eng*. 5(8): 926-940, 2021
3. Kanazawa S, Okada H, Hojo H, Ohba S, Iwata J, Komura M, Hikita A, Hoshi K. Mesenchymal stromal cells in the bone marrow niche consist of multi-populations with distinct transcriptional and epigenetic properties. *Sci Rep.* 11(1):15811, 2021
4. Fujiyabu T, Sakai T, Kudo R, Yoshikawa Y, Katashima T, Chung UI, and Sakumichi N. Temperature Dependence of Polymer Network Diffusion. *Physical Review Letters* 127, 237801, 2021
5. Ishikawa S, Kamata H, Chung UI, Saka T. On-demand retrieval of cells three-dimensionally seeded in injectable thioester-based hydrogels. *RSC Advances* 11, 23637, 2021
6. Yoshikawa Y, Sakumichi N, Chung UI, and Sakai T. Negative Energy Elasticity in a Rubberlike Gel. *Physical Review X* 11, 11045, 2021
7. Tang J, Katashima T, Li X, Mitsukami Y, Yokoyama Y, Chung UI, Shibayama M, Sakai T. Effect of Nonlinear Elasticity on the Swelling Behaviors of Highly Swollen Polyelectrolyte Gels. *Gels* 7, 25, 2021

Laboratory of Microenvironmental and Metabolic Health Sciences

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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 research assistant, one project assistant, one project researcher, one visiting researcher, six graduate students (four for the doctoral course and two for the master course), four external researchers, and one research assistant conducted the researches together during the year of 2022.

This laboratory belongs to the Department of Social Medicine, cooperates to the Departments International Health Sciences and Social Public Health, and is engaged in education and research on relationships. The laboratory is also associated with the Department of Cellular Signaling, the Molecular Cell Biology.

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 A_2 (PLA_2) 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 previously reported that PLA2G5 (sPLA$_2$-V), secreted from hypertrophic white adipocytes during 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), and that PLA2G2D (sPLA$_2$-IID), secreted from M2-like macrophages in white adipose tissue, releases ω3 polyunsaturated fatty acids (PUFAs) to promote cold-induced adipocyte browning and thermogenesis (Sato et al, *Cell Rep,* 2020). In addition, we have recently found that PLA2G2E (sPLA$_2$-IIE) is highly induced in brown and beige adipocytes in response to cold and that its genetic deletion leads to partial impairment of adipocyte browning and thermogenesis.

Choline supplies methyl groups for regeneration of methionine and the universal methyl donor *S*-adenosylmethionine (SAM) in the liver. Although membrane PC is the main cellular reservoir for choline, the pathway for hepatic PC catabolism that generates free endogenous choline remains unexplored. We found that PNPLA7, a lysophospholipase that catalyzes the hydrolysis of lysophosphatidylcholine (LPC) to glycerophosphocholine (GPC), is crucial for this pathway. *Pnpla7*-deficient mice show marked decreases in hepatic GPC, choline, betaine and SAM, accompanied by various signs of methionine insufficiency including impaired triglyceride storage and secretion, hypoglycemia, increased energy expenditure, reduced fat mass with adipocyte browning, and decreased epigenetic histone and DNA methylation. Accordingly, *Pnpla7*$^{-/-}$ mice are lean, display growth retardation, and die prematurely. We further found that mice lacking PNPLA8 (iPLA$_2$γ), which acts as PLA$_1$/A$_2$, recapitulate most of these phenotypes, suggesting that PNPLA8 lies upstream of PNPLA7. Thus, the methyl group flux from choline endogenously generated through PC breakdown by the PNPLA8-PNPLA7 axis is essential for liver functions and systemic energy homeostasis (submitted). In addition, skeletal muscle-specific *Pnpla7*-deficient mice develop sarcopenia-like symptoms over 6 months.

2) Skin diseases

Lipids play crucial roles in skin homeostasis and diseases. We previously reported that PLA2G2F (sPLA$_2$-IIF), which is specifically expressed in epidermal keratinocytes, mobilizes lysoplasmalogen, a unique lysophospholipid that promotes epidermal hyperplasic diseases such as psoriasis and skin cancer (Yamamoto et al, *J Exp Med,* 2015), and that PNPLA1, a member of the intracellular iPLA$_2$ family whose mutations cause autosomal recessive congenital ichthyosis, acts as a transacylase to produce ω-*O*-acylceramide, an essential lipid component for skin barrier function (Hirabayashi et al, *Nat Commun,* 2017). PLA2G4E (cPLA$_2$ε), which is expressed in epidermal keratinocytes, exhibits a unique *N*-acyltransferase activity that transfers a fatty acid from the *sn*-1 position of PC to the amino group of phosphatidylethanolamine (PE) to give rise to *N*-acyl PE (NAPE), a precursor of the non-canonical bioactive lipid *N*-acylethanolamine (NAE). *Pla2g4e*-deficient mice display exacerbation of psoriasis with marked reduction of various NAE species, suggesting that PLA2G4E plays a role in putting a brake on psoriasis by generating the anti-inflammatory lipid mediator NAE (Liang et al, *FASEB J* 2022). In addition to the skin, PLA2G4E participates in NAE generation in the skeletal muscle and stomach (Murakami et al, *Biochem Pharm* 2022).

PLA2G3 (sPLA$_2$-III) is expressed in epidermal keratinocytes and its global or skin-specific deletion leads to perturbation of skin barrier function due to fragile cornified envelope and loosened epidermal tight junction. Accordingly, following topical antigen challenge, global or skin-specific *Pla2g3*-deficient mice display more severe atopic dermatitis-like symptoms with increased expression of type 2 cytokines, serum IgE levels, eosinophil infiltration, scratching behavior, and disturbed skin microbiota. Global or skin-specific deletion of EP4 (PGE$_2$ receptor) or FP (PGF$_{2\alpha}$ receptor) largely if not solely recapitulate these phenotypes, and treatment with FP or EP4 agonists rescues skin abnormalities in *Pla2g3*-deficient mice. Moreover, global or skin-specific *Pla2g3*-deficient mice exhibit more severe asthma following topical antigen challenge. These results

suggest that PLA2G3-driven PGE_2-EP4/$PGF_{2\alpha}$-FP signaling in keratinocytes plays an important role in skin barrier formation and thereby skin homeostasis, perturbation of which leads to exacerbation of atopic march.

3) Allergic and other immunological diseases

We previously reported that PLA2G3, an $sPLA_2$ isoform secreted from mast cells (MCs), promotes MC maturation by driving the paracrine PGD_2 circuit in cooperation with microenvironmental fibroblasts (Taketomi et al, *Nat Immunol* 2013; Taketomi et al, *Cells* 2021) and that PAF-AH2, a unique PLA_2 that hydrolyzes oxidized phospholipids, ensures optimal MC activation and thereby allergic responses through producing unique EPA/DHA metabolites (ω3 epoxides) (Shimanaka et al, *Nat Med* 2017). Furthermore, we have recently found that PLA2G3 is also coupled with another lipid mediator, lysophosphatidic acid (LPA), which acts in concert with PGD_2 to facilitate MC maturation.

PLA_2 subtypes that regulate T cell immunity are unknown. By transcriptional and functional screening of PLA_2 enzymes expressed in T cells, we have found that PLA2G12A ($sPLA_2$-XIIA) is induced in Th17 cells and participates in Th17 differentiation. Global and $CD4^+$ T cell-specific *Pla2g12a*-deficient mice have lower psoriatic inflammation with decreased Th17 and γδT cells in the skin and draining lymph nodes. We are now analyzing a particular lipid mediator that acts downstream of PLA2G12A in inducing Th17 immunity.

4) Gut microbiota

Despite the restricted intestinal expression of PLA2G2A ($sPLA_2$-IIA) in BALB/c mice, its genetic deletion leads to amelioration of skin carcinogenesis. Metagenome, transcriptome and metabolome analyses have revealed that *Pla2g2a* deficiency alters the gut microbiota, accompanied by notable changes in the intestinal expression of genes related to immunity and metabolism as well as the levels of various blood metabolites and fecal bacterial lipids, suggesting that PLA2G2A contributes to shaping of the gut microbiota (Miki et al, *JCI Insight*, 2022). *Pla2g2a*$^{-/-}$ mice also display an alteration in passive cutaneous anaphylaxis (Taketomi et al, *Metabolites* 2022). These results highlight a new aspect of PLA2G2A as a modulator of gut microbiota, perturbation of which affects distal skin responses. Furthermore, mice lacking PLA2G10 ($sPLA_2$-X), which is predominantly expressed in the colorectal epithelium, also have altered gut microbiota, and their systemic effects are now being analyzed.

5) Cancer

Extracellular vesicles (EVs) including exosomes act as intercellular communicators by transferring protein and microRNA cargoes, yet the role of EV lipids remains unclear. We have recently found that the pro-tumorigenic action of lymphoma-derived EVs is augmented via $sPLA_2$-driven lipid metabolism. Hydrolysis of EV phospholipids by PLA2G10 ($sPLA_2$-X), which is induced in a specific population of macrophages in Epstein-Barr virus (EBV)-induced lymphoma, increases the production of fatty acids, lysophospholipids and their metabolites. $sPLA_2$-treated EVs are smaller, self-aggregate, show better uptake, and increase cytokine expression and lipid mediator signaling in recipient tumor-associated macrophages. Lymphoma growth in EBV-infected mice is suppressed by a $sPLA_2$ inhibitor, while treating the mice with $sPLA_2$-modified EVs can reverse this phenotype. Overall, the $sPLA_2$-driven EV modification promotes tumor development (Kudo et al, *Cell Metab* 2022). It is anticipated that modification of EVs by $sPLA_2$s may occur universally in various cancers as well as in allergic and metabolic diseases, a possibility that is currently under investigation.

6) Infectious diseases

PLA2G2D expressed in dendritic cells and M2 macrophages attenuates anti-viral Th1 immunity by supplying ω3 PUFAs and PGD_2 (Miki et al, *J Exp Med* 2013). In collaboration with a foreign group, we have reported that *Pla2g2d* deficiency protects mice from pneumonia caused by coronavirus infection (Roy Wong et al, *Nature* 2022). Therefore, PLA2G2D may be an attractive drug target for treatment of COVID-19.

7) Neuronal and retinal diseases

Mutations in the *PNPLA6* gene cause neuronal and retinal degeneration such as hereditary spastic paraplegia (SPG39), Boucher-Neuhauser syndrome, Oliver-McFariane syndrome, and Laurence-Moon syndrome. PNPLA6 acts a phospholipase B (PLA_1/A_2 + lysophospholipase), hydrolyzing PC to give rise to two fatty acids and GPC, in cells. Intriguingly, neuron-specific deletion of PNPLA6 and its closest homolog PNPLA7 leads to neurodegenerative disorders similar to hereditary spastic paraplegia and that tamoxifen-

inducible eye-specific deletion of PNPLA6 results in retinal degeneration. Retinal degeneration in these mice can be prevented by eye drops of choline, a PC degradation product. Clarifying the regulatory roles of lipid metabolism driven by PNPLA6/PNPLA7 will shed light on the molecular mechanism underlying the PNPLA6-related neuronal and retinal disorders.

Furthermore, in collaboration with an external group, a particular $sPLA_2$ isoform that is induced after cerebral infarction is found to be involved in protection against neuronal damage by mobilizing a unique lipid metabolite (*submitted*).

2. Environmental Toxicology (Ohsako's group)

Ohsako found a new phenotype that was accidentally discovered in the course of a project using the famous Ahr-deficient mouse (AhrKO). AhrKO mice have long been reported to have phenotypes such as liver fibrosis, decreased fertility, and immune system dysfunction. Ahr is a gene essential for detoxification and excretion of carcinogens such as benzo[a]pyrene, which is a typical xenobiotic substance. Ahr is activated by binding to these ligands and induces down-stream genes for drug-metabolizing enzyme. However, Ahr has also been reported to regulate differentiation of the helper T-cells such as Th17/Treg through binding to its endogenous ligands. This suggests that Ahr is involved in autoimmune diseases. Ohsako found that AhrKO exhibited loose stools and melena at about 10 weeks of age, followed by obvious rectal prolapse and continued to survive. Compared to the wild type, AhrKO mice showed enlargement of the spleen and mesenteric lymph nodes, enlargement of the colon and marked inflammatory cell infiltration of the lamina propria. CD4+IL17+IFNγ-Th17 cells were significantly increased in the spleen, mesenteric lymph nodes, and colonic lamina propria, whereas there was no difference in CD4+Foxp3+Treg cells. In contrast to the finding above, previous reports have reported that Th17 differentiation is suppressed in spleen cells of Ahr-deficient mice. In addition, liver fibrosis did not cause clear lesions. By using metagenomic analysis, it was found that the content of the mouse colon in the SPF facility of Tokyo University of Science represents specific bacterial flora. Therefore, AhrKO was bred at the SPF facility of Japan CLEA Co., Ltd. from individual restored by IVF. In these mice inflammatory colitis was not observed. Additionally, it was found that there is a clear difference between the flora of Japan CLEA and those of Tokyo University of Science flora. These results suggested that specific gut microbiota that are supposed to produce Ahr endogenous ligands are involved in the development of the inflammatory bowel disease discovered in the AhrKO mice.

Teaching activities

The Laboratory of Microenvironmental and Metaboilic Health Sciences/ the Department of Cellular Signaling 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 medical students (M0). Four undergraduate students (three M2 students and one M4 student) participate in the Murakami's team throughout the year.

Publications

1. Miki Y, Taketomi Y, Kidoguchi Y, Yamamoto K, Muramatsu K, Nishito Y, Park J, Hosomi K, Mizuguchi K, Kunisawa J, Soga T, Boilard E, Gowda SGB, Ikeda K, Arita M, Murakami M. Group IIA secreted phospholipase A_2 controls skin carcinogenesis and psoriasis by shaping the gut microbiota. *JCI Insight.* 7, e152611, 2022.
2. Doré E, Joly-Beauparlant C, Morozumi S, Mathieu A, Lévesque T, Allaeys I, Duchez AC, Cloutier N, Leclercq M, Bodein A, Payré C, Martin C, Petit-Paitel A, Gelb MH, Rangachari M, Murakami M, Davidovic L, Flamand N, Arita M, Lambeau G, Droit A, Boilard E. The

interaction of secreted phospholipase A_2-IIA with the microbiota alters its lipidome and promotes inflammation. *JCI Insight*. 7, e152638, 2022.

3. Kudo K, Miki Y, Carreras J, Nakayama S, Nakamoto Y, Ito M, Nagashima E, Yamamoto K, Higuchi H, Morita S, Inoue A, Aoki J, Ando K, Nakamura N, Murakami M, Kotani A. Secreted phospholipase A_2 modifies extracellular vesicles and accelerates B-cell lymphoma. *Cell Metab.* 34, 1-19, 2022.
4. Roy Wong LY, Zheng J, Wilhelmsen K, Li K, Ortiz ME, Schnicker NJ, Pezzulo AA, Szachowicz PJ, Klumpp K, Aswad F, Rebo J, Narumiya S, Murakami M, Meyerholz DK, Fortney K, McCray PB, Perlman S. Eicosanoid signaling as a therapeutic target in middle-aged mice with severe COVID-19. *Nature*. 605, 146-151, 2022.
5. Shibata T, Kawana H, Nishino Y, Ito Y, Sato H, Onishi H, Kano K, Inoue A, Taketomi Y, Murakami M, Kofuji S, Nishina H, Miyazawa A, Kono N, Aoki J. Abnormal male reproduction and embryonic development induced by downregulation of a phospholipid fatty acid-introducing enzyme Lpgat1 in zebrafish. *Sci Rep*. 12, 7312, 2022.
6. Liang L, Takamiya R, Miki Y, Heike K, Taketomi Y, Sugimoto N, Yamaguchi M, Shitara H. Nishito Y, Kobayashi T, Hirabayashi T, Murakami M. Group IVE cytosolic phospholipase A_2 limits psoriatic inflammation by mobilizing the anti-inflammatory lipid *N*-acylethanolamine. *FASEB J.* 36, e22301, 2022.
7. Taketomi Y, Miki Y, Murakami M. Old but new: Group IIA phospholipase A_2 as a modulator of gut microbiota. *Metabolites*. 12, 352, 2022. (Review)
8. Taketomi Y, Murakami M. Regulatory roles of phospholipase A_2 enzymes and bioactive lipids in mast cell biology. *Front. Immunol*. 13, 923265, 2022. (Review)
9. Murakami M, Takamiya R, Miki Y, Sugimoto N, Nagasaki Y, Suzuki-Yamamoto T, Taketomi Y. Segregated functions of two cytosolic phospholipase A_2 isoforms (cPLA$_2$α and cPLA$_2$ε) in lipid mediator generation. *Biochem. Pharmacol*. 203, 115176, 2022. (Review)
10. Ekuban A, Zong C, Ekuban FA, Kimura Y, Takizawa R, Morikawa K, Kinoshita K, Ichihara S, Ohsako S, Ichihara G. Role of macrophages in cytotoxicity, reactive oxygen species production and DNA damage in 1,2-dichloropropane-exposed human cholangiocytes in vitro. *Toxics*. 9, 128, 2021.
11. Ekuban FA, Zong C, Takikawa M, Morikawa K, Sakurai T, Ichihara S, Itoh K, Yamamoto M, Ohsako S, Ichihara G. Genetic ablation of Nrf2 exacerbates neurotoxic effects of acrylamide in mice. *Toxicology*. 456, 152785, 2021.

Laboratory of Animal Resources

Professor

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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 6 teaching staffs, 6 technical support staffs, an administrative staff, 2 assistant laboratory animal technicians, 2 assistant clerks and 2 temporary staffs (veterinarian, support staff). In addition, about 15 contracted employees are involved in animal breeding and maintenance of the animal facility.

The laboratory animals in our facility include macaque monkeys, dogs, swine, rabbits, rats, mice, and marmosets. The number of registered users of our facility was 637 at the end of academic year 2021.

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 the synaptic plasticity, activity dependent formation of neuronal circuitry, and neuropsychiatric disorders. We generate knockout mice and transgenic mice of signal transduction molecules including the glutamate receptors and mammalian target of rapamycin

(mTOR). We also try to generate murine and marmoset models for human genetic diseases.

1. Establishment of model marmosets for fragile X syndrome

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 introduced guide RNAs for *FMR1* (fragile X mental retardation 1) gene encoding fragile X mental retardation protein (FMRP) and Cas9 proteins into marmoset embryos. We obtained mutant marmosets which carried mutations in coding region of *FMR1* gene. *FMR1* mutant marmosets, which fail to express the FMRP protein, exhibit epileptic-like seizures and are lethal by 8 days of age. Heterozygotes for *FMR1* were successfully obtained by crossing a mosaic male individual carrying wild-type and mutant *FMR1* alleles with wild-type females. We are currently recording the movements and vocalizations of the heterozygote under spontaneous behavior to determine whether this animal is a model for Fragile X Syndrome.

2. Elucidating the neural basis of comforting behavior

Comforting 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 is observed as a comfort-like behavior. The division also attempted to detect comforting behavior in inbred mice and constructed an experimental system to see comforting behavior prominently and efficiently.

Although ASD patients are thought to have a tendency to have difficulty sharing feelings and emotions with others (lower levels of empathy), there is little biological evidence to support a causal relationship between such mental illness and lack of empathy. To elucidate the mechanism by which psychiatric disorders cause lack of empathy at the neural circuit and organism levels, we decided to investigate whether the lack of empathic behavior is observed in genetically engineered mouse models of psychiatric disorders that we developed previously, such as 22q11.2 deletion syndrome mouse models. Our study will reveal how having a genetic predisposition to mental illness affects comforting behavior, one of the empathic behaviors.

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, molecular analysis of vascular endothelial cells and pericytes (mural cells), which constitute the BBB, has not been elucidated well. Therefore, we aim to reveal the molecular mechanisms involved in vascular permeability and cancer brain metastasis by reconstituting the BBB in vitro using vascular endothelial cells, pericytes, and astrocytes and by genetically manipulating vascular endothelial cells in individual mice.

In vitro BBB model indicated the necessity of pericytes and astrocytes in brain metastasis. We established the brain metastatic cell line of marine lung cancer by repeating transplantation and isolation of brain metastasis in mice. The brain metastatic cells showed highly metastatic feature in our in vitro BBB model, although it could not successfully migrate without pericytes and astrocytes. The mice with endothelial cell-specific knockout of focal adhesion kinase (FAK) also indicated the different metastatic mechanism of brain metastasis compared to the trunk metastasis. The brain metastasis is not suppressed by endothelial cell-specific knockout of FAK, although it has been reported that endothelial cell-specific knockout mice of FAK show the inhibition of metastasis in the trunk.

Now we plan to elucidate the specific mechanism needed for brain metastasis by analyzing the interaction of cancer cells with BBB, especially for the surrounding pericytes and astrocytes.

References

1. Arioka Y, Shishido E, Kushima I, Suzuki T, Saito R, Aiba A, Mori D, and Ozaki N. Chromosome 22q11.2 deletion causes PERK-dependent vulnerability in dopaminergic neurons. ***EBio Medicine,*** 63, 103138, 2021.
2. Saito R, Miyoshi C, Koebis M, Kushima I, Nakao K, Mori D, Ozaki N, Funato H, Yanagisawa M, and Aiba A. Two novel mouse models mimicking minor deletions in 22q11.2 deletion syndrome revealed the contribution of each deleted region to psychiatric disorders. ***Mol Brain,*** 14(1), 68, 2021.
3. Kawarada L, Fukaya M, Saito R, Kassai H, Sakagami H, and Aiba A. Telencephalon-specific Alkbh1 conditional knockout mice display hippocampal atrophy and impaired learning. ***FEBS Lett,*** 595(12), 1671-1680, 2021.
4. Yamasaki M, Aiba A, Kano M, and Watanabe M. mGluR1 signaling in cerebellar Purkinje cells: Subcellular organization and involvement in cerebellar function and disease. ***Neuro-pharmacology,*** 194, 108629, 2021.
5. Hasegawa K, Takenaka N, Tanida K, Chan MP, Sakata M, Aiba A, and Satoh T. Atrophy of White Adipose Tissue Accompanied with Decreased Insulin-Stimulated Glucose Uptake in Mice Lacking the Small GTPase Rac1 Specifically in Adipocytes. ***Int J Mol Sci,*** 22(19), 10753, 2021.
6. Abe Y, Nakao H, Goto M, Tamano M, Koebis M, Nakao K, and Aiba A. Efficient marmoset genome engineering by autologous embryo transfer and CRISPR/Cas9 technology. ***Sci Rep,*** 11(1), 20234, 2021.

Laboratory of Molecular Radiology

Professor

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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 two facilities are elected from our section. This year, the hospital radioisotope research facility was continued to be closed to prepare the opening of the new facility in the newly-constructed Clinical Research Building.

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 SCYP3-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 immune-fluorescence. 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 1α 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.

In addition to Rad51, 5 Rad51 paralogs, Rad54, Rad54B, and Rad52 are also involved in early stages of HR. While Rad51 paralogs and Rad54 were shown to assist the Rad51-dependent cascade, the involvement of Rad54B in HR is not closely associated with Rad51and Rad54. This fact led us to hypothesize that Rad54B has a role distinct from other HR factors. We found that levels of Rad54B are inversely correlated with protein levels of p53 both after DNA damage and Rad54B knockout cells. Protein interaction analysis revealed that Rad54B promotes proteasome-dependent degradation of p53 by directly binding to MDM2/MDMX, an E3 ubiquitin ligase complex targeting p53. Furthermore, we found that overexpression of Rad54B facilitates genomic instability by negatively regulating cell-cycle checkpoints medicated by p53. Consistent with this biological function, high levels of Rad54B were shown to correlate with poor prognosis in colorectal cancers. In addition, increases in its expression are also observed in other types of cancers.

Although the role of Rad52 in yeast homologous recombination is established, its role in mammals remains unclear. Its functional analysis in normal human epithelial cells revealed that Rad52 is involved in the processing of R-loop, the structure formed by RNA and DNA at the site of a DNA double-strand

break. This finding suggests that Rad52 plays a role in transcription-associated homologous recombination, providing novel insight into DNA repair at transcribed regions.

Thus, our studies on the mechanisms underlying HR contribute to the establishment of important strategies against cancer. Radiation 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. If we will understand the details of the repair pathways, the molecules in this pathway will be the therapeutic targets. From the clinical point of view, we are continuing the research exploring the principle in this field.

Publications

1. Hosoya N, Miyagawa K. Synaptonemal complex proteins modulate the level of genome integrity in cancers. Cancer Sci, 112:989-996, 2021.
2. Hosoya N, Miyagawa K. Implications of the germline variants of DNA damage response genes detected by cancer precision medicine for radiological risk communication and cancer therapy decisions. J Radiat Res, 62 (Suppl. 1): i44–i52, 2021.
3. Ochi Y, Yoshida K, Huang YJ, Kuo MC, Nannya Y, Sasaki K, Mitani K, Hosoya N, Hiramoto N, Ishikawa T, Branford S, Shanmuganathan N, Ohyashiki K, Takahashi N, Takaku T, Tsuchiya S, Kanemura N, Nakamura N, Ueda Y, Yoshihara S, Bera R, Shiozawa Y, Zhao L, Takeda J, Watatani Y, Okuda R, Makishima H, Shiraishi Y, Chiba K, Tanaka H, Sanada M, Takaori-Kondo A, Miyano S, Ogawa S, Shih LY. Clonal evolution and clinical implications of genetic abnormalities in blastic transformation of chronic myeloid leukaemia. Nat Commun, 12:2833, 2021.
4. Kobayashi H, Makise N, Shinozaki-Ushiku A, Ishibashi Y, Ikegami M, Kohsaka S, Ushiku T, Oda K, Miyagawa K, Aburatani H, Mano H, Tanaka S. Scapular angiomatoid fibrous histiocytoma with EWSR1-CREB1 fusion in an adult patient. Case Rep Orthop, 30:9434222, 2021.
5. Fukasawa T, Yoshizaki A, Ebata S, Yoshizaki-Ogawa A, Asano Y, Enomoto A, Miyagawa K, Kazoe Y, Mawatari K, Kitamori T, Sato S. Single-cell-level protein analysis revealing the roles of autoantigen-reactive B lymphocytes in autoimmune disease and the murine model. Elife, 10:e67209, 2021.

Laboratory of Biomedical Informatics

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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 Patho-physiological 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

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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 effective ness 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 Tokyo Medical Dental University 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. The department is also in charge of the administration of the OSCE (objective structured clinical examination). 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) and class/curriculum surveys 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

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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.

International Cooperation

Since March 2020, a faculty member has participated as an expert in the "Information Gathering and Confirmation Survey on Higher Education and Vocational Education in Indonesia" conducted by JICA. However, the pandemic of COVID-19 greatly affected the progress of the survey. The dispatch of the faculty remains suspended.

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: We explore how education and policies in the health and medical fields should be based through participation in international cooperation projects in countries mainly in Asia. We try to become the core center for the research in this area by conducting practical efforts as an expert on the project under Japan International Cooperation Agency, by accumulating experiences in the area such as evaluation method, policy recommendation, coordination of stakeholders, and by disseminating the research results.

(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 decision is made. Various changes are

seen in the concept of assessment itself. As for research, development of work-based assessment methods, verification of reliability and validity, improvement of methods for setting pass / fail judgment criteria are examples.
(3) Research related to ACP (advance care planning): We are continuing research on 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: We currently work for how to train the professionals contributing to community-based integrated care system.

References

1. Osamu Nomura, Hirotaka Onishi, Yoon Soo Park, Nobuaki Michihata, Tohru Kobayashi, Kazunari Kaneko, Tetsushi Yoshikawa, Akira Ishiguro & Japan Pediatric Society Steering Committee of Board Examination (2021). Predictors of performance on the pediatric board certification examination. BMC medical education, 21(1), 1-7.

Global Nursing Research Center

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Introduction and Organization

With a falling birthrate and a super-aging society, Japan is in need of a paradigm shift toward a medical and nursing care that supports the 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 difficulty of the living and brings a self-reliant way of life to the Japanese nation. Nursing, which plays a central role in providing care, must develop into a new field as 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 a 'medical and nursing care that supports.’ 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 a 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 both the development of the necessary human resources that will be required to promote this transdisciplinary research, as well as 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 that ranges from fundamental research to studies with

commercial application.

Thus, the Global Nursing Research Center has been established as an affiliated research center, which is the first of its kind in nursing science. The GNRC will continue to execute the following three goals:

1) Establish an innovative nursing research field based on transdisciplinary integration;

2) Carry out cutting-edge research and present it to the world with young researchers pursuing the sciences;

3) Build up a foundation of these new fields through repeated research trials that will strengthen the new research and education systems.

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, constructing Japan-origin nursing theories that support high quality practices, and making policy proposals.'

3. Achievements

In 2021, one international joint research project and one industry-government-academia research project were undertaken. In addition, 72 original English articles were published.

Executing Innovative Research

1. International Invited Faculty

In 2021, we had one Project Professor: Prof. Ardith Doorenbos: Professor in Biobehavioral Nursing Science, University of Illinois, Chicago, and invited two researchers: Prof. Seonae Yeo: Professor of School of Nursing, University of North Carolina at Chapel Hill, and Prof. Carolina D. Weller: Professor, Head of Wound Research Group, Monash University.

2. Post-doctoral Program

Post-doctoral (PD) researchers engage in focused research projects, the findings of which will be made known to the public. In addition, PD researchers must take five essential seminars that cover comprehensive research knowledge, skills, and global awareness for the training of youth for leadership.

These five required seminars are, as follows: (1) How to Write a Research Paper in English, (2) Leadership in Nursing Research, (3) Qualitative Research Methods, (4) Health Quality Outcome Research, and (5) Introductory Seminar to Nursing Science and Engineering.

Further, there are an additional five optional seminars: (1) Skin Assessment, (2) Ultrasonography, (3) Qualitative Sketch Techniques, (4) Biological Nursing, and (5) 3D Measurement and Modeling Hands-on Seminar for Nursing Science and Engineering.

In 2021, two PD researchers participated in this program, and completed the program.

3. Other Universities' Young Researchers

In 2021, our PD seminars and lectures were opened to young researchers from other universities, and by the end of the year, a total of 1541 participants attended.

Building Future Research

1. Global Nursing Research Center Fund

The Global Nursing Research Center Fund was continued for the purpose of fostering young researchers.

Accomplishments

1. Astrada A, Nakagami G, Minematsu T, Goto T, Kitamura A, Mugita Y, et al. Concurrent validity of biofilm detection by wound blotting on chronic wounds. J Wound Care. 2021;30(Sup4): S4-13.
2. Kataoka Y, Kunimitsu M, Nakagami G, Koudounas S, Weller DC, Sanada H. Effectiveness of ultrasonic debridement on reduction of bacteria and biofilm in patients with chronic wounds: A scoping review. Int Wound J. 2021;18(2):176-86.

3. Koyanagi H, Kitamura A, Nakagami G, Kashiwabara K, Sanada H, Sugama J. Local wound management factors related to biofilm reduction in the pressure ulcer: a prospective observational study. Jpn J Nursing Sci. 2021; 18(2):e12394.2020.
4. Hasegawa Y, Yoshida M, Sato A, Fujimoto Y, Minematsu T, Sugama J, et al. A change in temporal muscle thickness is correlated with past energy adequacy in bedridden older adults: A prospective cohort study. BMC Geriatrics. 2021; 21(1):182.
5. Matsumoto M, Nakagami G, Kitamura A, Kurita M, Suga H, Miyake T, et al. Ultrasound assessment of deep tissue on the wound bed and periwound skin: a classification system using ultrasound images. J Tissue Viability. 2021;30(1): 28-35.
6. Matsumoto M, Fujioka M, Okada T, Naka Y, Amemiya A, Matsushima E, et al. Evaluation of bowel preparation before colonoscopy by ultrasonographic monitoring of colonic fecal retention: A case series. Med Ultrason. 2021; 23(2):147-52.
7. Abe-Doi M, Murayama R, Komiyama C, Sanada H. Changes in the subcutaneous tissue of catheterization site from the precatheterization state to the onset of anticancer drug-induced induration: a case report. Clin Case Rep. 2021; 9(1): 57.
8. Murayama R, Abe-Doi M, Kogure T, Takahashi T, Kanno C, Ishigaki M, et al. The influence of peripheral intravenous catheterization on the sleep quality of ophthalmic inpatients: An observational study. J Nurs Sci Eng. 2021;8:134-42.
9. Oe M, Tsuruoka K, Ohashi Y, Takehara K, Noguchi H, Mori T, et al. Prevention of diabetic foot ulcers using a self-monitoring device smartphone and mobile thermography: Case study. J Wound Care. 2021;30(2):116-9.
10. Morisaki-Nakamura M, Suzuki S, Kobayashi A, Kita S, Sato I, Iwasaki M, et al. Development and validation of a Japanese version of the TRANSITION-Q. Pediatr. Int. 2021;63(3):270-8.
11. Eltaybani S, Igarashi A, Yamamoto-Mitani N. Palliative and end-of-life care education in prelicensure nursing curricula: A nationwide survey in an Arab country. Nurse Educ Today. 2021;96:104644.
12. Sakka M, Kita S, Sato I, Soejima T, Eguchi H, Tokita M, et al. Reliability and validity of the Japanese version of the Caregiving Interface Work Scale in employed Japanese family caregivers. Geriat Gerontol Int. 2021;21(2): 254-61.
13. Sari DW, Minematsu T, Yoshida M, Noguchi-Watanabe M, Tomida S, Kitamura A, et al. Validity of skin blot examination for albumin and nerve growth factor β to detect itching of the skin in Indonesian older adults. J Tissue Viability. 2021;30(1):42-50.
14. Eltaybani S, Yamamoto-Mitani N, Ninomiya A, Igarashi A. The association between nurses' burnout and objective care quality indicators: a cross-sectional survey in long-term care wards. BMC Nurs. 2021;20(1):34.
15. Kida R, Togari T, Yumoto Y, Ogata Y. The association between workplace social capital and authentic leadership, structural empowerment, and forms of communication as antecedent factors in hospital nurses: a cross-sectional multilevel approach. J Nurs Manag. 2021;29(3): 508-17.
16. Inoue M, Kunie K, Takemura Y, Ichikawa N, Kida R. The influence of learning circumstances and on-the-job opportunities for professional growth on perceived person-environment fit among hospital nurses: a longitudinal study. J Nurs Manag. Forthcoming.
17. Saiki M, Kunie K, Takemura Y. Nursing assistants' desired roles, perceptions of nurses' expectations, and effect on team participation: A cross-sectional study. J Nurs Manag. Forthcoming.
18. Piao X, Tsugawa S, Takemura Y, Ichikawa N, Kida R, Kunie K, et al. Disability Weights Measurement for 17 Diseases in Japan: A Survey Based on Medical Professionals. Econ Anal Policy. 2021;70:238-48.
19. Takahashi Y, Kunie K, Takemura Y. The lasting impacts of work-attendance decisions of health care employees under uncertainty: Japanese hospital nurses' experiences outside the

evacuation zone after the nuclear accident. The Journal of Organization and Discouse. Forthcoming.
20. 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. Jpn J Nurs Sci. 2021;18:e12436.
21. Abe-Doi M, Murayama R, Komiyama C, Tateishi R, Sanada H. Effectiveness of ultrasonography for peripheral catheter insertion and catheter failure prevention in visible and palpable veins. J Vasc Access. 2021, DOI: 10.1177/11297298211022078
22. Tanaka S, Kunie K, Takemura Y, Ichikawa N, Kida R. Exploring nurses' clinical reasons for bed transfers in acute care wards: An observational study. J Nurs Manag. (accepted 26 Apr. 2021) doi: 10.1111/jonm.13352
23. Kawaguchi S, Takemura Y, Takehara K, Kunie K, Ichikawa N, Komagata K, et al. Relationship between teams' Leader–Member Exchange characteristics and psychological outcomes for nurses and nurse managers: A cross-sectional study in Japan. SAGE Open Nursi 2021; 7: 1-11.
24. Tanaka S, Kunie K, Takemura Y, Ichikawa N, Kida R. The patterns and reasons for changing bed placement in multi-bed rooms in acute care settings. J So Nurs Pract. (accepted 24 Jun. 2021)
25. Ishii K, Takemura Y, Ichikawa N, Kunie K, Kida R. The relationship between nursing groups' organizational socialization and nurses' perception of organizational learning sub-processes: A cross-sectional study in hospital wards. Team Perform Manag. (accepted 15 Jul. 2021) doi: 10.1108/TPM-01-2021-0002
26. Hikita N, Batsaikhan E, Sasaki S, Haruna M, Yura A, Oidovsuren O. Factors Related to Lacking Knowledge on the Recommended Daily Salt Intake among Medical Professionals in Mongolia: A Cross-Sectional Study. Int J Environ Res Public Health. 2021;18(8):3850.
27. Tahara-Sasagawa E, Ota Y, Matsuzaki M, Shimpuku Y, Oishi T. Visualization of midwifery education in 109 countries on a world map: Secondary analysis of the data from the International Confederation of Midwives (ICM). J Jpn Acad Midwif. 2021;35(1):48-56.
28. Murakami M, Yonezawa K, Shimizu S, Haruna M, Sasagawa E, Usui Y. Newborn-oriented and environmental factors for newborns' skin barrier functions. Jpn J Nurs Sci. 2021. (Accepted)
29. Koudounas S, Minematsu T, Mugita Y, Tomida S, Nakai A, Nakagami G et al. 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. J Nurs Sci Engineer. 2021; 8: 220-9.
30. Hsu W, Minematsu T, Nakagami G, Koudounas S, Tomida S, Nakai A et al. Identification of microRNAs responsive to shear loading in rat skin. Int Wound J. Online ahead of print. 2021.
31. Kunimitsu M, Nakagami G, Kitamura A, Minematsu T, Mugita Y, Ogai K et al. Dissemination of microbiota between wounds and the beds of patients with pressure injuries: A cross-sectional study. Wound Pract Res. 2021; 29(2): 70-6.
32. Astrada A, Nakagami G, Minematsu T, Goto T, Kitamura A,Mugita Y et al. Concurrent validity of biofilm detection by wound blotting on chronic wounds. J Wound Care. 2021; 30 (Sup4): S4-13.
33. Tsukatani T, Minematsu T, Dai M, Tamai N, Nakagami G, Sugama J et al. Polymorphism analysis of candidate risk genes for pressure injuries in older Japanese patients: A cross-sectional study at a long-term care hospital. Wound Repair Regen. 2021; 29(5): 741-51.
34. Sawada U, Shimazu A, Kawakami N, Miyamoto Y, Speigel L, Leiter MP. The Effects of the Civility, Respect, and Engagement in the Workplace (CREW) Program on Social Climate and Work Engagement in a Psychiatric Ward in Japan: A Pilot Study. Nursing Reports. 2021; 11(2):320-330.
35. Iida M, Watanabe K, Imamura K, Sakuraya A, Asaoka H, Sato N, Nozawa K, Kawakami N. Development and validation of the Japanese version of the team job crafting scale for nurses. Research in Nursing & Health. 2021; 44(2): 329-43.

36. Asaoka H, Sasaki N, Imamura K, Kuroda R, Tsuno K, Kawakami N. Changes in COVID-19 measures in the workplace: 8-month follow-up in a cohort study of full-time employees in Japan. Journal of Occupational Health. 2021; 63(1): e12273.
37. Sasaki N, Asaoka H, Kuroda R, Tsuno K, Imamura K, Kawakami N. Sustained poor mental health among healthcare workers in COVID-19 pandemic: A longitudinal analysis of the four-wave panel survey over 8 months in Japan. Journal of occupational health. 2021; 63(1): e12227.
38. Eltaybani S, Ahmed FR. Family satisfaction in Egyptian adult intensive care units: A mixed-method study. Intensive Crit Care Nurs. 2021 Oct;66:103060.
39. Sumikawa Y, Honda C, Yoshioka-Maeda K, Yamamoto-Mitani N. Characteristics of COVID-19-related free telephone consultations by public health nurses in Japan: A retrospective study. Healthcare. 2021 Aug 9;9(8):1022.
40. Matsumoto H, Maeda A, Igarashi A, Weller C, Yamamoto-Mitani N. Dementia education and training for the general public: a scoping review. Gerontology & Geriatrics Education.
41. Honda C, Naruse T, Yamana H, Yamamoto-Mitani N. Infant Injury Prevention Education for Pregnant Women Attending Antenatal Class: A Quasi-Experimental Study. Int. J. Environ. Res. Public Health 2021, 18(17), 9393
42. Matsumoto M, Tamai N, Miura Y, Okawa Y, Yoshida M, Igawa Y, et al. Evaluation of a point-of-care ultrasound education program for nurse educators. J Contin Educ Nurs. 2021;52(8): 375-81.
43. Matsumoto M, Karube M, Nakagami G, Kitamura A, Tamai N, Miura Y, et al. Development of an automatic ultrasound image classification system for pressure injury based on deep learning. Appl Sci. 2021;11(17):7817.
44. Kunimitsu M, Nakagami G, Kitamura A, Minematsu T, Mugita Y, Ogai K et al. Dissemination of microbiota between wounds and the beds of patients with pressure injuries: A cross-sectional study. Wound Pract Res. 2021; 29(2): 70-6.
45. Astrada A, Nakagami G, Minematsu T, Goto T, Kitamura A,Mugita Y et al. Concurrent validity of biofilm detection by wound blotting on chronic wounds. J Wound Care. 2021; 30 (Sup4): S4-13.
46. Qin Q, Oe M, Ohashi Y, Shimojima Y, Imafuku M, Dai M, Nakagami G, Yamauchi T, Yeo S, Sanada H. Factors associated with the local increase of skin temperature, 'hotspot,' of callus in diabetic foot: A cross-sectional study. Journal of Diabetes Science and Technology. 2021: 19322968211011181.
47. Mugita Y, Minematsu T, Nakagami G, Sanada H. Promoting effect of acylated homoserine lactone on the healing of tissue damage in incontinence-associated dermatitis model rats. Journal of Wound Care. 2021.
48. Kunimitsu M, Kataoka Y, Nakagami G, CWeller DC, Sanada H. Factors related to the composition and diversity of wound microbiota investigated using culture-independent molecular methods: a scoping review. Drug Discoveries & Therapeutics. 2021;15(2):78-86.
49. Mugita Y, Koudounas S, Nakagami G, Weller C, Sanada H. Assessing Absorbent Products' Effectiveness for the Prevention and Management of Incontinence-associated Dermatitis Caused by Urinary, Faecal or Double Adult Incontinence: A Systematic Review. Journal of Tissue Viability. 2021.
50. Haba D, Nakagami G, Minematsu T, Sanada H. Low-frequency vibration promotes AMPK-mediated glucose uptake in 3T3-L1 adipocytes. Heliyon. 2021.
51. Yoshinaga N, Nakagami G, Fukahori H, Shimpuku Y, Sanada H, Sugama J. Initial Impact of the COVID-19 Pandemic on Time Japanese Nursing Faculty Devote to Research: Cross-Sectional Survey. Japan Journal of Nursing Science. 2021.
52. Honda C, Naruse T, Yamamoto-Mitani N. Pregnant Women's Intentions to Implement Safety Practices for Preventing Infant Injury: A Cross-Sectional Study. International journal of environmental research and public health. 2021; 18(1):24.

53. Sumikawa Y, Yamamoto-Mitani N. Transitional care during COVID-19 pandemic in Japan: calls for new strategies to integrate traditional approaches with information and communication technologies. BioScience Trends. Published online 2021.
54. Matsumoto H, Kawagoe M, Hotta S. Older Adults Used Fewer Home Care Services during the COVID-19 Pandemic: Findings from a Secondary Analysis of an Urgent Survey in Japan. Ann Geriatr Med Res. 2021;25(4):286-293.
55. 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. Progress in Community Health Partnerships: Research, Education, and Action(in Press).
56. Matsumoto H, Maeda A, Igarashi A, Weller C, Yamamoto-Mitani N. Dementia education and training for the general public: a scoping review. Gerontol Geriatr Educ. 2021. Doi: 10.1080/02701960.2021.1999938. Epub ahead of print.
57. Eltaybani S, Abdelhalim GE, Abdelgawad ME. Nursing students' and educators' experience with e-learning during a pandemic: An online survey. Nurs Forum. 2021;56(4):878-888. doi: 10.1111/nuf.12634.
58. Yonezawa K, Haruna M, Ohya Y. Impact of skin conditions of infants on their mothers' quality of life. J Neonatal Nurs. 2021. Doi.org/10.1016/j.jnn.2021.10.012
59. 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. 2021. doi.org/10.1016/j.jnn.2021.10.012
60. Shiraishi M, Matsuzaki M, Tsunematsu R, Watanabe S, Kobayashi R & Haruna M. Effects of Individual Dietary Intervention on Nutrient Intake in Postpartum Japanese Women: A Randomized Controlled Trial. Nutrients. 2021; 13(9): 3272.
61. Tamai N, Minematsu T, Sanada H. Changes in scalp epidermal thickness using in vivo reflectance confocal microscopy in breast cancer patients undergoing chemotherapy: a case series. J Nurs Sci Eng. 2021;8:143-150.
62. Koudounas S, Mugita Y, Minematsu T, Nakagami G, Weller C, Sanada H. Does the presence of bacterial urinary infection contribute to the development of incontinence-associated dermatitis? A scoping review. Journal of Tissue Viability. 2021;30(2):256-261.
63. Miura Y, Tamai N, Kitamura A, Yoshida M, Takahashi T, Mugita Y, et al. Diagnostic accuracy of ultrasound examination in detecting aspiration and pharyngeal residue in patients with dysphagia: A systematic review and meta-analysis. Japan Journal of Nursing Science. 2021;18:e12396.
64. Sari WD, Minematsu T, Yoshida M, Noguchi-Watanabe M, Tomida S, Kitamura A, et al. Validity of skin blot examination for albumin and nerve growth factor β to detect itching of the skin in Indonesian older adults. Journal of Tissue Viability. 2021;30(1):42-50.
65. Takahashi T, Shintani Y, Murayama R, Noguchi H, Abe-Doi M, Koudounas S, et al. Ultrasonographic measurement of blood flow of peripheral vein in the upper limb of healthy participants: a pilot study.Journal of the Japanese Society of Wound, Ostomy, and Continence Management. 2021;25(3).
66. Minematsu T, Dai M, Tamai N, Nakagami G, Urai T, Nakai A, et al. Risk scoring tool for forearm skin tears in Japanese older adults: A prospective cohort study. Journal of Tissue Viability. 2021;30(2):155-160.
67. Shimizu S, Yonezawa K, Haruna M, Sasagawa E, Hikita N, Sanada H, et al. Relationship between the skin barrier function of 2-week old infants after bathing and facial skin problems during the first 6 weeks of life: A prospective observational cohort study. The Japan Journal of Nursing Science. 2021:e12408.
68. Nakagami G, Yokota S, Kitamura A, Takahashi T, Morita K, Noguchi H, et al. 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.

69. Takahashi T, Murayama R, Abe-Doi M, Miyahara M, Kanno C, Nakagami G, et al. Catheter failure in the administration of hyperosmotic drugs through a peripheral vein and vascular selection: A retrospective cohort study. Drug Discoveries & Therapeutics. 2021;15(5):236-240.
70. Maeda T, Tamai N, Minematsu T, Noguchi H, Yabunaka K, Nakagami G, et al. The relationship between pressure injuries and dynamic buttock pressure distributions during performance in wheelchair basketball athletes. Wound Practice and Research. 2021.
71. Kitamura A, Nakagami G, Minematsu T, Kunimitsu M, Sanada H. Establishment of an infected wound model by bacterial inoculation on wound surface in rats. J Nurs Sci Eng. 2021;9: 1-8.
72. Takizawa C, Kitamura A, Nakagami G, Matsumoto M, Hayashi C, Kawasaki A, et al. The relationship between the temperature distribution detected by thermography and suspected deep tissue injuries. Jpn J PU. 2021.

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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. 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.*

2. Morishima R, Kumakura K, Usami S, Kanehara A, Tanaka M, Okochi N, Nakajima N, Hamada J, Ogawa T, Ando S, Tamune H, Nakahara M, Jinde S, Kano Y, Tanaka K, Hirata Y, Oka A, Kasai K: Medical, welfare, and educational challenges and psychological distress in parents caring for an individual with 22q11.2 deletion syndrome: A cross-sectional survey in Japan. *American Journal of Medical Genetics Part A*. 2022 Jan;188(1):37-45. doi: 10.1002/ajmg.a.62485. Epub 2021 Sep 3. PMID: 34480405.
3. Kaji N, Ando S, Nishida A, Yamasaki S, Kuwabara H, Kanehara A, Satomura Y, Jinde S, Kano Y, Hiraiwa-Hasegawa M, Igarashi T, Kasai K: Children with special health care needs and mothers' anxiety/depression: findings from the Tokyo Teen Cohort study. *Psychiatry Clin Neurosci*. 2021 Dec; 75(12):394-400. doi: 10.1111/pcn.13301. doi: 10.1111/pcn.13301. PMID: 34549856.

Office of International Academic Affairs

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Status and functions

The Office of International Academic Affairs (OIAA) is under the direct authority of the Dean of the Faculty of Medicine. Its three most important roles, as defined by the Committee on International Academic Affairs, are facilitating 1) international academic exchange, 2) international academic and research agreements, and 3) education and research activities.

Activities

This report details the activities of the OIAA during the 2021-22 academic year (1 April 2021 through 31 March 2022).

1. International Academic Exchange

1.1 Student guidance on education and research

The OIAA assists international students in applying for various scholarships, and the OIAA on-campus screening committee evaluates applicants for scholarships that require university recommendations. To promote friendship among international students, the OIAA organizes a get-together every spring at Capo Pellicano, a restaurant in the Faculty of Medicine Experimental Research Building. Unfortunately, the 2021-22 event was cancelled because of the COVID-19 pandemic.

The OIAA oversees undergraduate clinical training (elective clerkships) for international students at the University of Tokyo Hospital; however, border restrictions in Japan forced many cancellation of elective clerkships scheduled, resulting in only two students being hosted in 2021-22.

1.2 Guidance on short-term and long-term overseas study programs for medical students and researchers at the University of Tokyo

The OIAA provides guidance and information on study abroad 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.

As of March 2020, the University of Tokyo Faculty of Medicine has agreements for exchange programs—which provide one to two months of clinical training—with the University of Pennsylvania, Johns Hopkins University, University of Michigan, University of Hawaii, Seoul National University, National Taiwan University, National University of Singapore, Karolinska Institute and Ludwig Maximilian University of Munich. The OIAA nominates qualified students for each university and assists in their preparation for study abroad.

Although students were nominated for electives scheduled for April through July 2021, the pandemic caused the host institutions to cancel these electives; only two students—those nominated for National Taiwan University—could complete their elective.

1.3 Support for overseas training of graduates

The OIAA assists graduates in preparing documents for applications to graduate schools and other institutions abroad and in obtaining medical licensure in other countries. During 2021-22, the OIAA assisted in preparing Medical Student Performance Evaluations for two applicants.

2. International Academic and Research Agreements

During the 2021-22 academic year, the interdepartmental agreement with the University of Munich was renewed. We continued interaction with strategic partnership universities such as the University of Chicago and National Taiwan University, including jointly hosting workshops online, which was possible during the COVID-19 pandemic.

3. Education and Research Activities

Dr. Florence Ene supervised and taught the Medical English I/II courses.

David Kipler trained graduate and undergraduate students in writing research articles and making oral presentations in English.

Dr. Keiko Nanishi served as a lecturer in the School of International Health, where she supervised graduate students and conducted research on international health.

Publications

1. Nanishi K, Green J, Hongo H. Development of the breastfeeding support scale to measure breastfeeding support from lay and professional persons, and its predictive validity in Japan. PeerJ. 2021 Jul 27;9:e11779.
2. Shibanuma A, Ansah EK, Kikuchi K, Yeji F, Okawa S, Tawiah C, Nanishi K, Addei S, Williams J, Asante KP, Oduro A, Owusu-Agyei S, Gyapong M, Asare GQ, Yasuoka J, Hodgson A, Jimba M; Ghana EMBRACE Implementation Research Project Team. Evaluation of a package of continuum of care interventions for improved maternal, newborn, and child health outcomes and service coverage in Ghana: A cluster-randomized trial. PLoS Med. 2021 Jun 25;18(6): e1003663.
3. Kikuchi K, Gyapong M, Shibanuma A, Asah E, Okawa S, Addei S, Nanishi K, Tawiah C, Yasuoka J, Yeji F, Oduro A, Owusu-Agyei S, Quansah-Asare G, Hodgson A, Jimba M; Ghana EMBRACE Implementation Research Team. EMBRACE intervention to improve the continuum of care in maternal and newborn health in Ghana: The RE-AIM framework-based evaluation. J Glob Health. 2021 Mar 27;11:04017.
4. Binns CW, Lee MK, Maycock B, Torheim LE, Nanishi K, Duong DTT. Climate Change, Food Supply, and Dietary Guidelines. Annu Rev Public Health. 2021 Apr 1;42:233-255.
5. Nanishi K, Hongo H, Tada K. Does giving infant formula to prevent cow's milk allergy hinder breast-feeding? J Allergy Clin Immunol. 2021 Mar;147(3):1118.

MD Scientist Training Program

Professor and Director

Kenzo Hirose, 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), and Prof. Haruhiko Bito (2015-2020), the Program currently consists of its director Prof. Kenzo Hirose and 3 staff members, Yuki Sugaya (assistant professor), Takeshi Sawada (assistant professor) and Yoshitaka Kurikawa (project assistant professor), and over 100 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 100 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 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. However, in 2021, the pandemic of COVID-19 prevented students from doing research abroad. Instead, 9 students participated in international and domestic online conferences to present their research. We also support exposure to clinical training in foreign hospitals with the Osamu Otsubo Tetsumon Fellowship. Unfortunately, due to the COVID-19 pandemic in the destination country, most of the students were not able to travel abroad. Therefore, 8 fellows studied cutting-edge medical care in domestic hospitals instead. One fellow gained invaluable experience as a student clinical clerk in a university hospital in Taiwan.

2) Organizing an MD scientist training program retreat

A MDSTP retreat was held on February 2 and 13, 2022 at Tetsumon Memorial Hole to present ongoing research progress in a closed meeting among peers. More than 50 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. The previous retreat was held in Nagoya in 2019, 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. 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.

The MSDTP also currently cooperates with 11 other universities in eastern Japan to organize annual

research students' retreats. In 2021, the annual summer retreat was held online under the auspices of Yokohama City University. More than 90 people participated in the retreat and presented their ongoing research progress and plans.

Activities (2021)

The number of registered students: 150 (3rd and 4th grade: 73, 5th and 6th: 77)

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: 5 lectures
Medical Research Communications: 62 lectures

Presentation of research progress: 2 (the retreat of MD scientist training program in the University of Tokyo and the annual research students' retreats with universities in eastern Japan)

The number of students receiving travel supports for research: 9 (including support for international and domestic online conference)

The number of students receiving Osamu Otsubo Tetsumon Fellowship: 9

The number of Year 6 students who passed their honors thesis defense: 2 (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 http://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 400m^2 areas, including about 70m^2 of a permanent gallery and 230m^2 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 143,701 people had visited by the end of FY2019. Since Mar. 2020, our museum has been temporarily closed due to COVID-19 pandemic

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 / Vice Dean)
Masaomi Nangaku, M.D., Ph.D.

Vice Director of OHRS (Professor)
Akira Akabayashi, 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://www.u-tokyo-ohrs.jp/
Top page of online application system: https://u-tokyo.bvits.com/esct/

Introduction and Organization

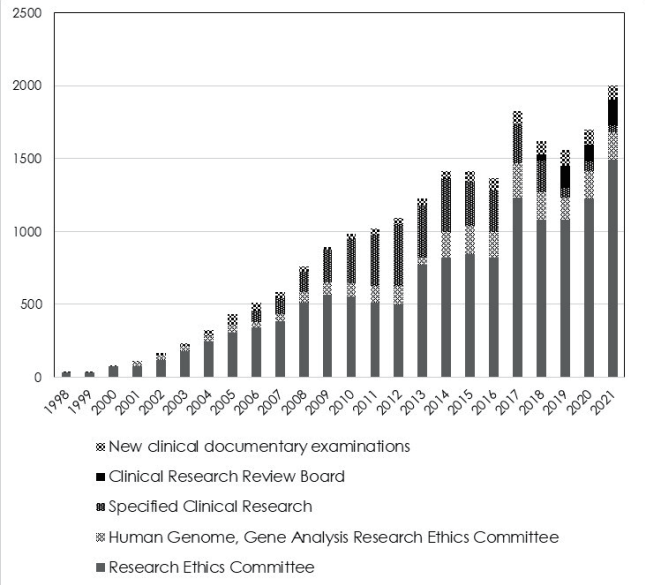
The Office for Human Research Studies (OHRS) was established in October 2009 for the advancement of research ethics standards. OHRS aims to protect the rights, health, and dignity of research participants. Based on this principle, OHRS is providing research ethics support services to researchers at Graduate 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 2021

- Research Ethics Committee (except for clinical trial, GCP):
  350 new applications, 1137 minor alterations of approved studies
- Clinical Research Review Board:174
- New clinical documentary examinations: 99



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. 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 2021 with 3255 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 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.

The Office for Clinical Practice and Medical Education

Professor

Masato Eto, M.D., Ph.D.

Research Associate

Shoko Horita, M.D., Ph.D.

Homepage https://igaku-kyoiku.m.u-tokyo.ac.jp/training.html

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.