

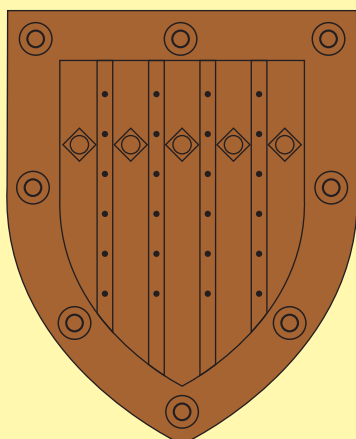
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ANNUAL REPORT OF
THE GRADUATE SCHOOL OF MEDICINE
AND
THE FACULTY OF MEDICINE
THE UNIVERSITY OF TOKYO
REPORTS FOR THE PERIOD April 2020 — March 2021



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ANNUAL REPORT OF THE GRADUATE SCHOOL OF
MEDICINE

THE FACULTY OF MEDICINE

THE UNIVERSITY OF TOKYO

REPORTS FOR THE PERIOD April 2020-March 2021

Introduction

This is volume 143(the edition of year 2021) 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, 2021

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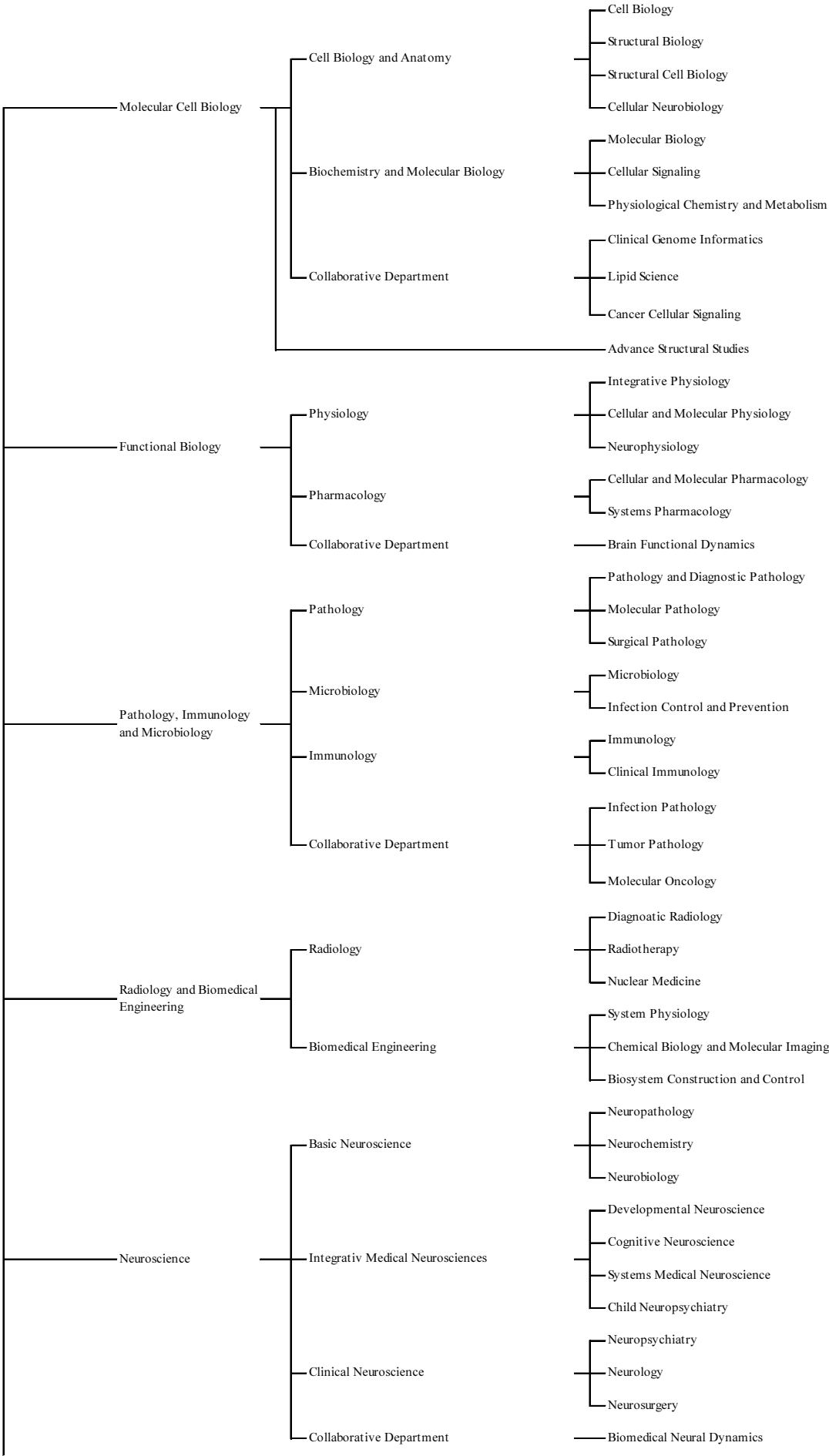
History

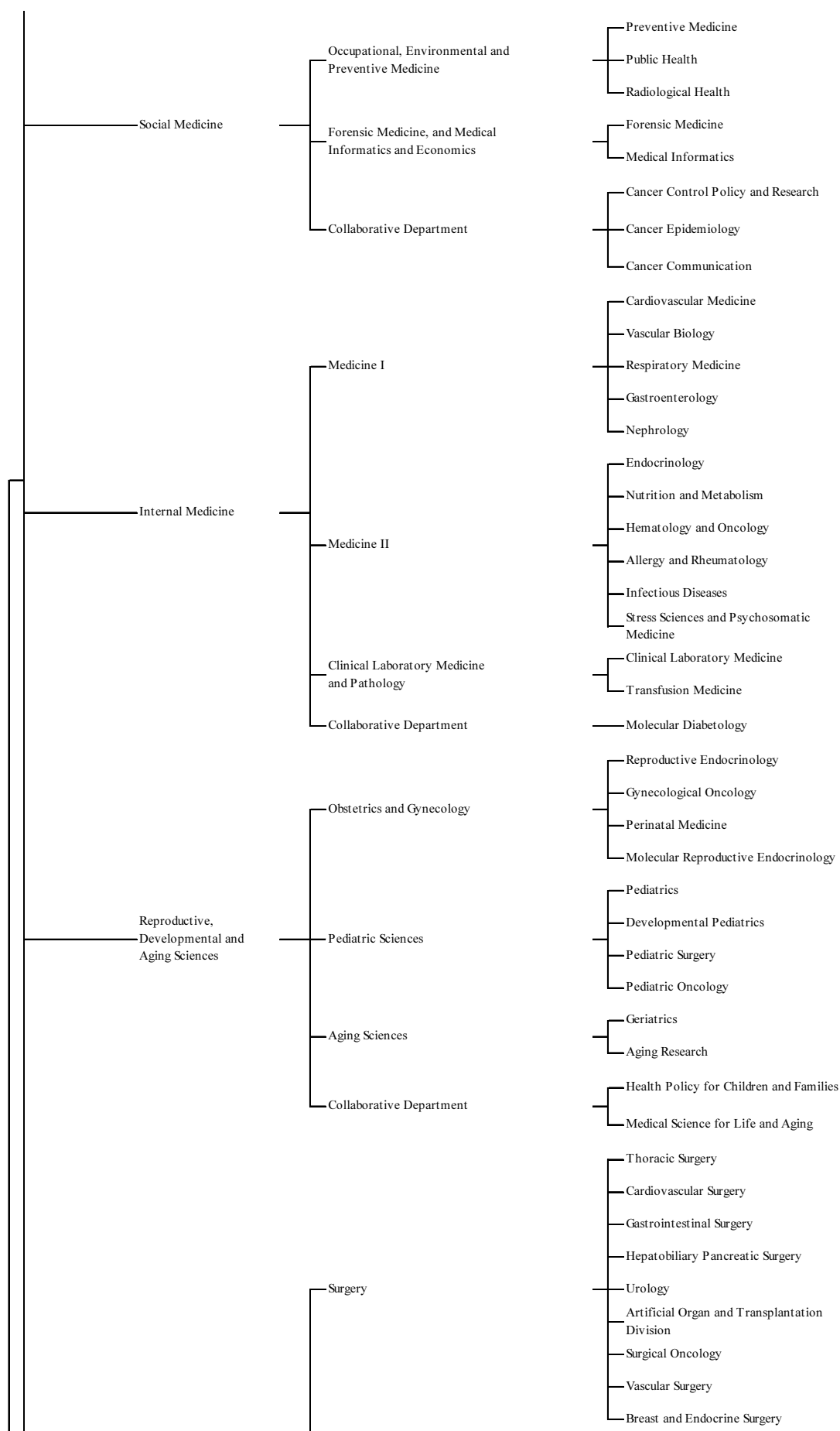
1858	May	Practitioners, trained in Dutch (European) medicine in Edo (Tokyo), laid out money to establish the Shutojo (vaccination center) in Kanda Mitamagaie.
	Nov.	Shutojo was destroyed in a fire that had spread from Kanda Aioicho. Shutojo continued its operations at other sites such as the residence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

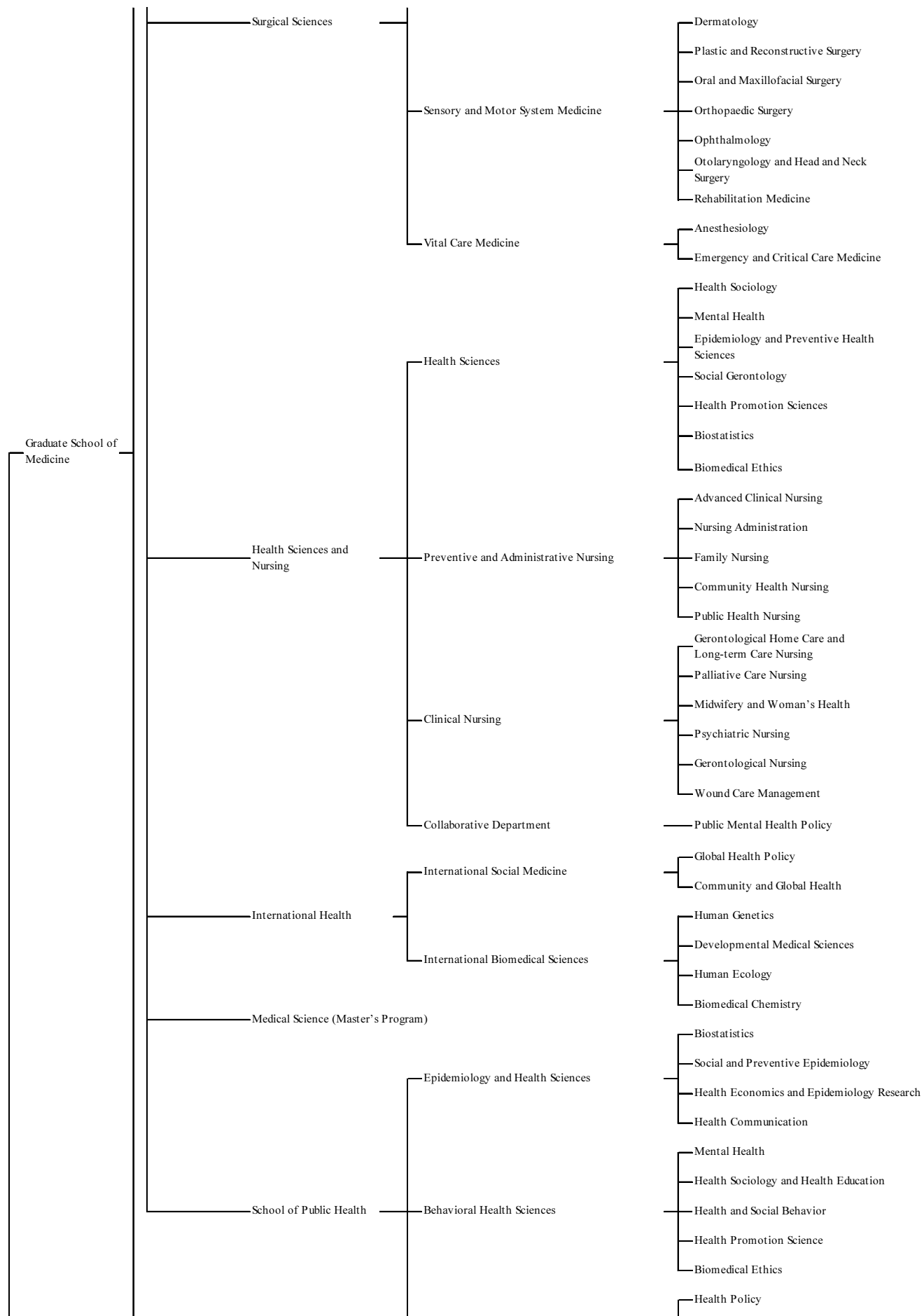
- Jul. The Graduate School was founded, and the Division of Medical Doctor Biological Science was established. The Brain Research Laboratory became the Brain Research Institute of the Faculty of Medicine.
- 1956 Apr. The Midwives School was established.
- 1958 Apr. The Division of Pharmaceutical Sciences 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.

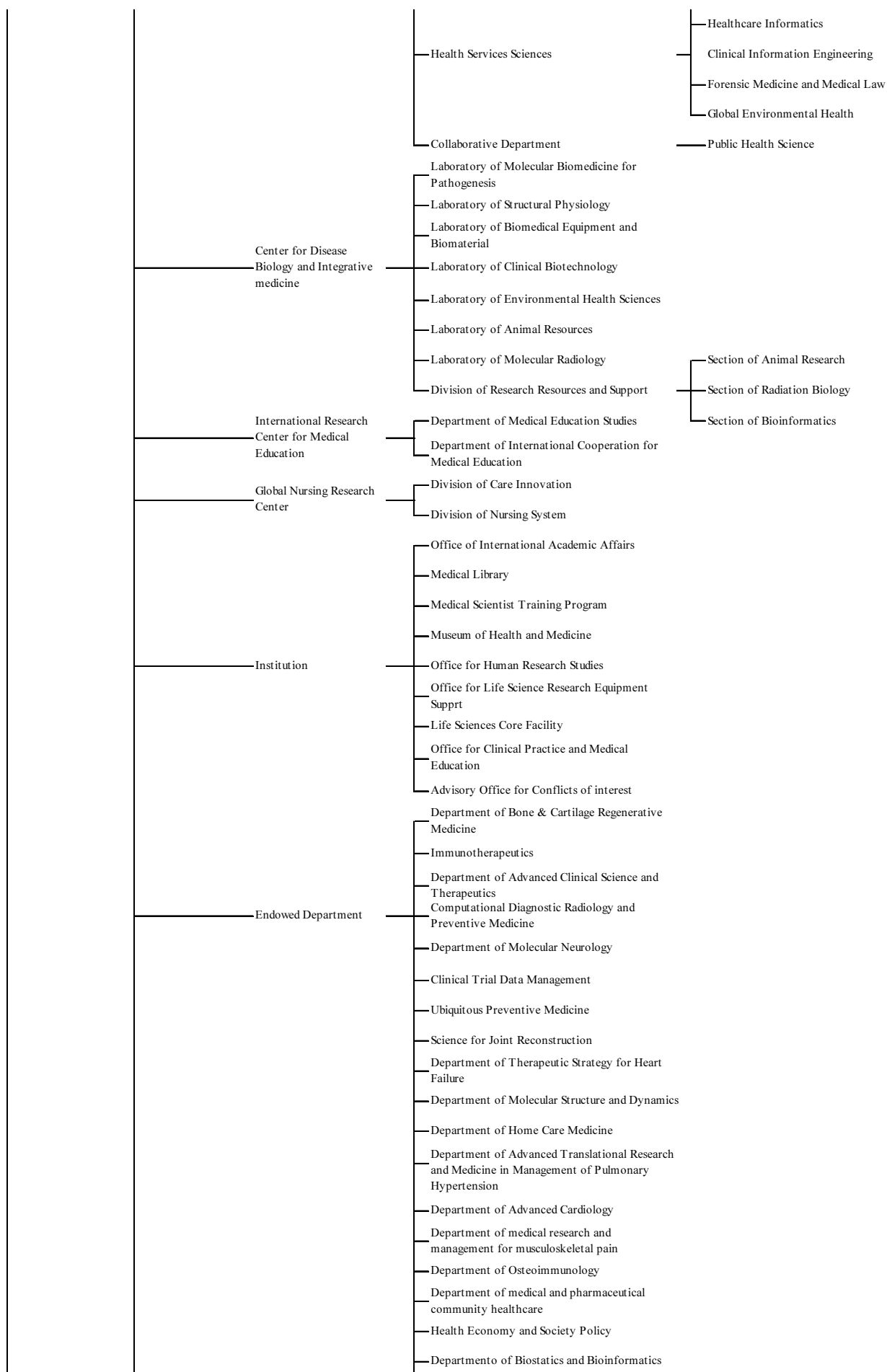
2000	Apr.	The International Research Center for Medical Education was established (A shared facility for education and research).
2001	Apr.	The University Branch Hospital was united with the University Hospital.
2002	Mar.	Nursing School and Midwives School was Closed.
2002	Mar.	Experimental Building (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.

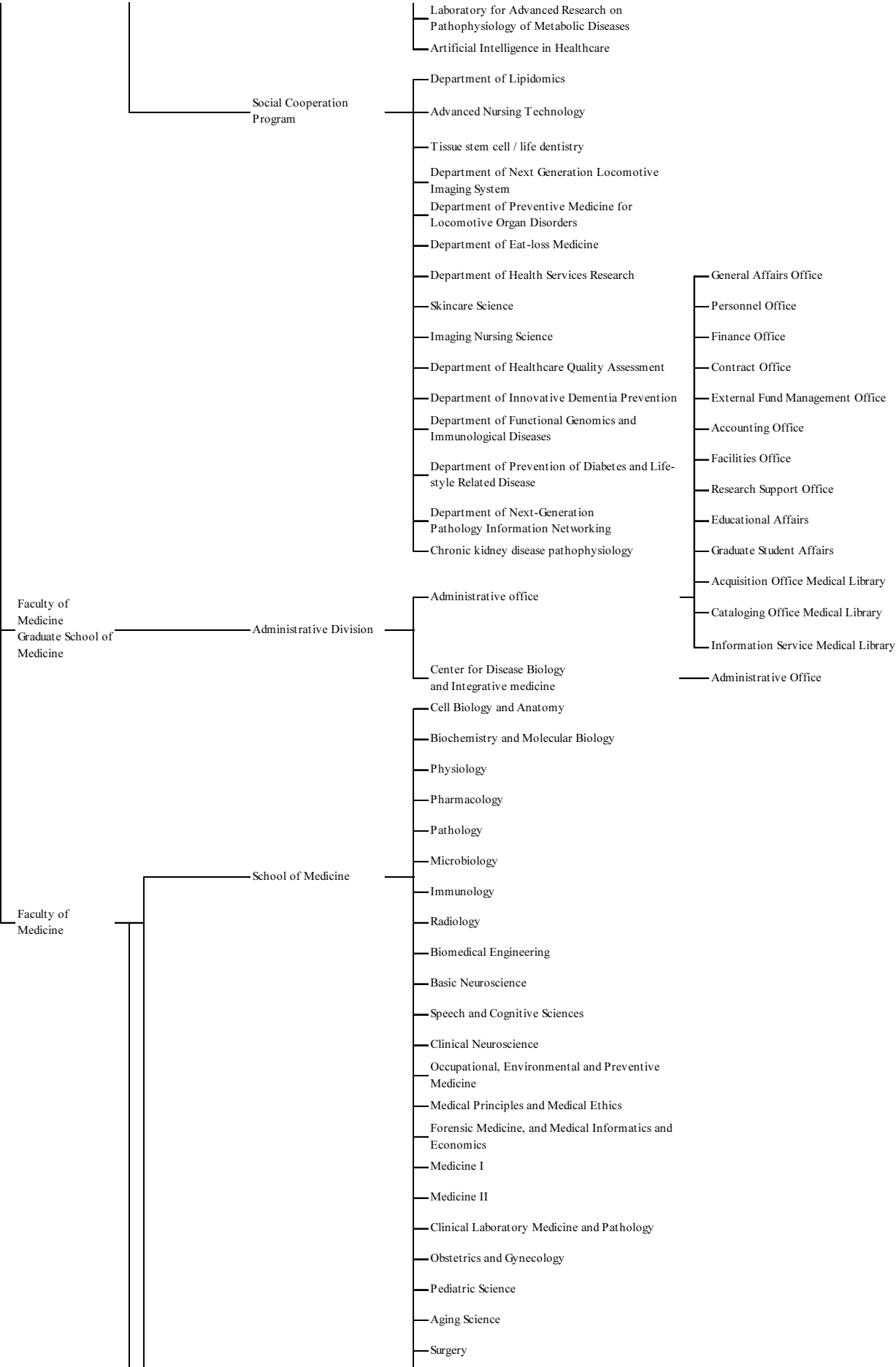
Organization Chart

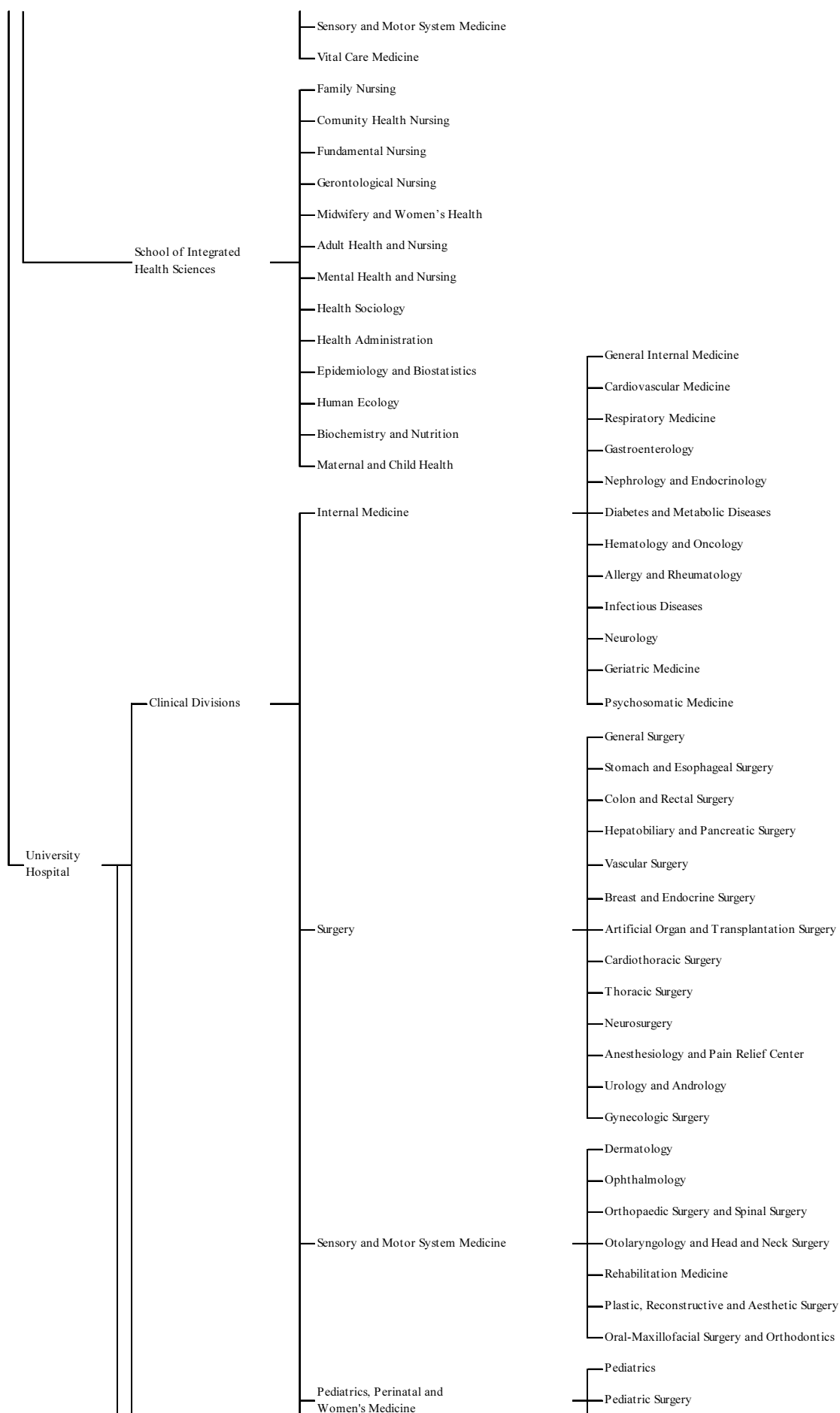


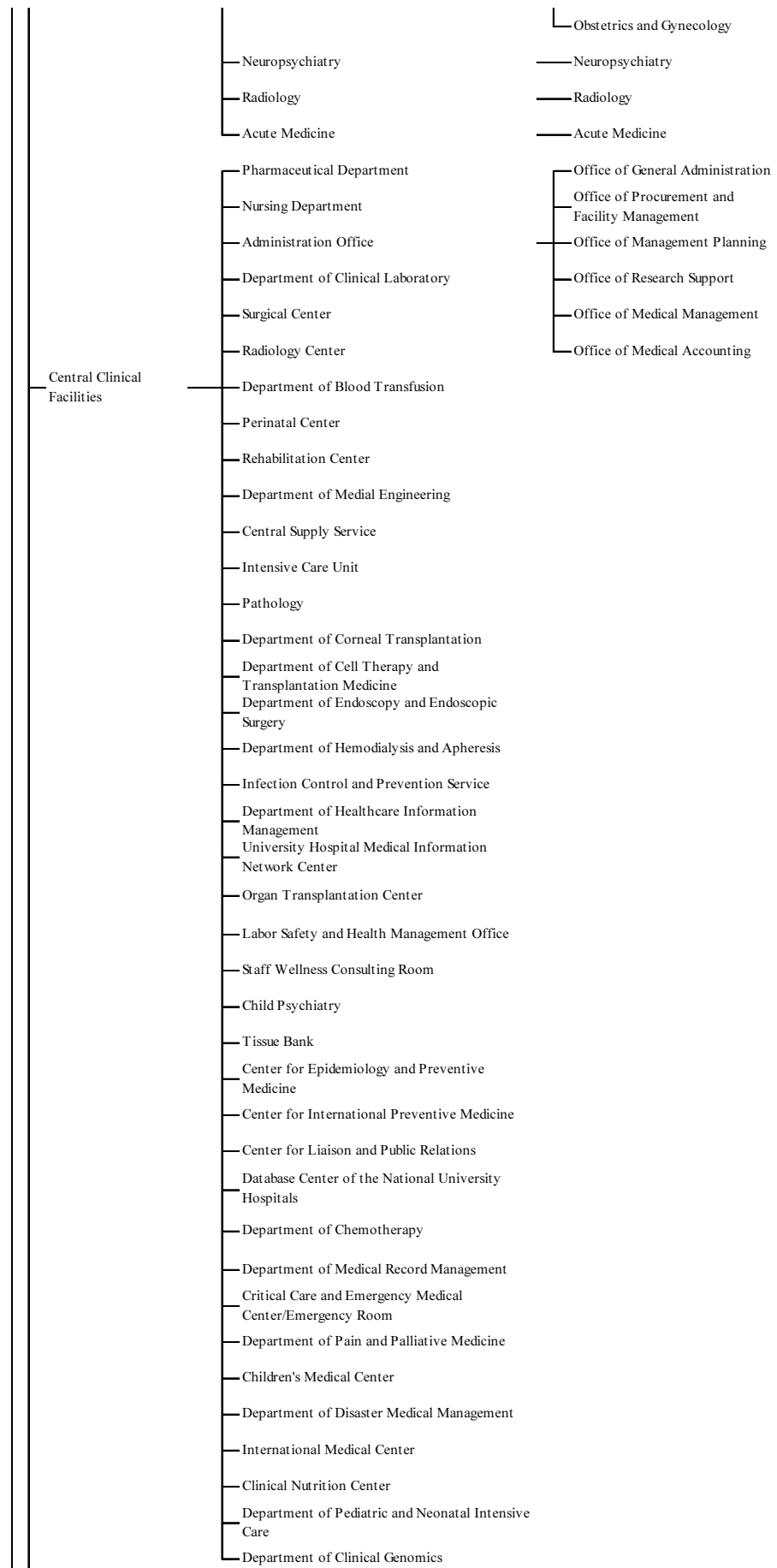


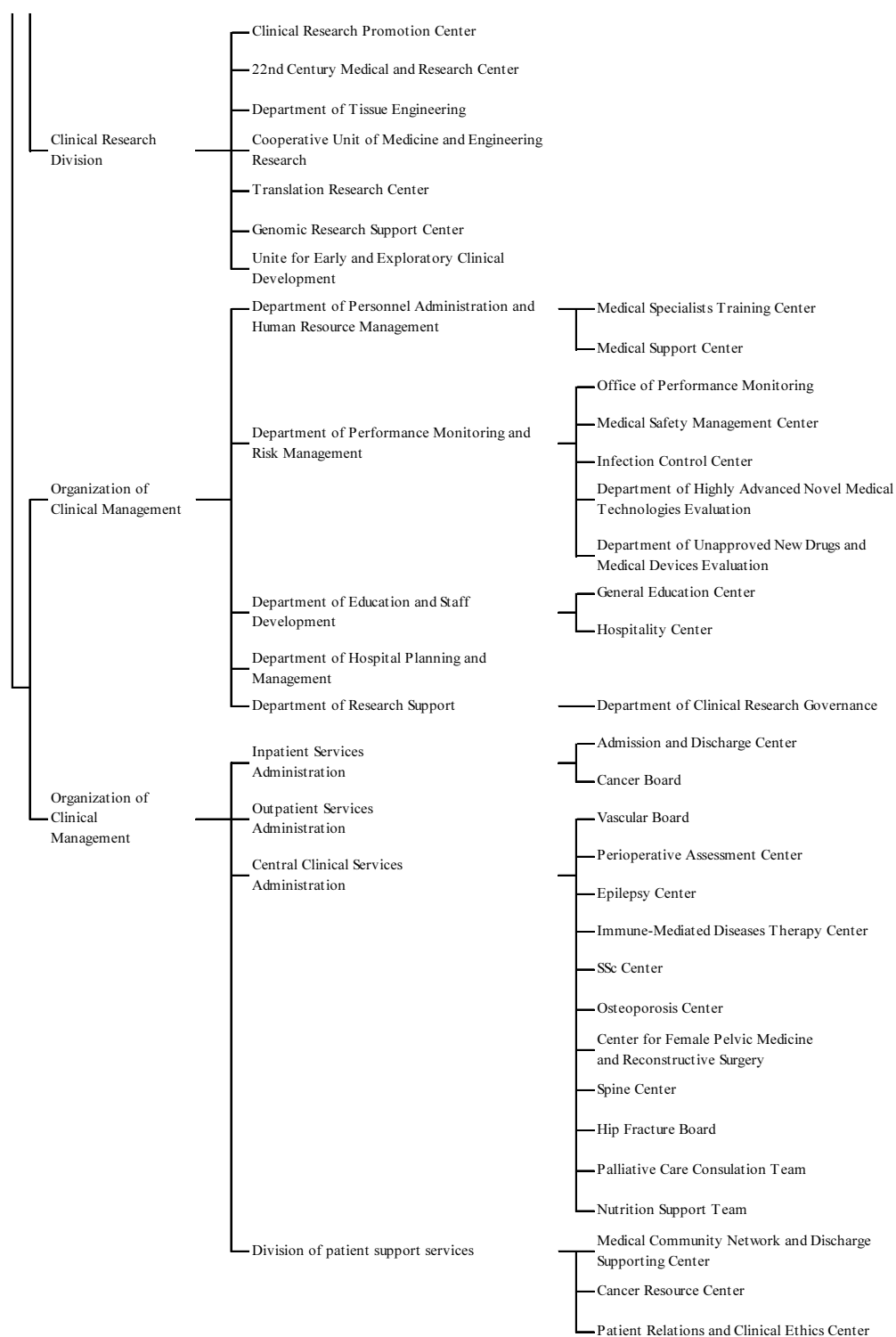












Teaching, Research, Secretarial and Administrative Staffs

Chief Members of Administration

Dean, Graduate School of Medicine (Dean, Faculty of Medicine)		Nobuhito Saito
Chairman, School of Health Sciences and Nursing		Noriko Yamamoto
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	Hirotarō Iwase
	Professor	Kazuhiko Ohe
Internal Medicine		
Department of Medicine I	Professor	Issei Komuro
	Professor	Takahide Nagase
	Professor	Kazuhiko koike
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	
	Professor	Yutaka Osuga
Department of Pediatric Science	Professor	Motohiro Kato
Department of Pediatric Surgery	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	Nobuhiko Haga
Department of Vital Care Medicine	Professor	Kanji Uchida
	Professor	Naoto Morimura
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	Kiyoko Kamibeppu
	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	Masashi Mizuguchi
	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	Hirotarō 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 Environmental 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

Professor Hiromi Sanada

Medical Library

Professor Hideo Yasunaga

International Academic Affairs

Professor Shinichi Sato

Medical Scientist Training Program

Professor Haruhiko Bito

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

Endowed Departments

Artificial Intelligence in Healthcare	Project Associate professor	Yoshimasa Kawazoe
Department of Bone & Cartilage Regenerative Medicine	Project Associate professor	Fumiko Yano
Cell & Tissue Engineering (Fujisoft)	Project Associate professor	Atsuhiko Hikita
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
Ubiquitous Preventive Medicine	Project Associate professor	Yuichi Ikeda
Science for joint reconstruction	Project Associate professor	Toru Moro
Therapeutic Strategy for Heart Failure	Project Associate professor	Masaru Hatano
Department of Molecular Structure and Dynamics	Project Professor	Nobutaka Hirokawa
Department of Advanced Translational Research and Medicine in Management of Pulmonary Hypertension	Project Associate professor	Haruhiro Toko
Department of 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
Health Economy and Society 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

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
Department of Healthcare Quality Assessment	Project Professor	Hiroaki Miyata
Department of Innovative Dementia Prevention	Project Associate professor	Tadafumi Hashimoto
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

University Hospital

Clinical Divisions

General Medicine	Head	Issei Komuro
Cardiovascular Medicine	Head	Issei Komuro
Respiratory Medicine	Head	Takahide Nagase
Gastroenterology	Head	Kazuhiko Koike
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	Nobuhiko Haga
Plastic, Reconstructive and Aesthetic Surgery	Head	Mutsumi Okazaki
Oral-Maxillofacial Surgery and Orthodontics	Head	Kazuto Hoshi
Pediatrics	Head	Naoto Takahashi
Pediatric Surgery	Head	Jun Fujishiro
Obstetrics and Gynecology	Head	Yutaka Ohsuga
Neuropsychiatry	Head	Kiyoto Kasai
Radiology	Head	Osamu Abe
Acute Medicine	Head	Naoto Morimura
Central Clinical Facilities		
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	Nobuhiko Haga
Department of Medical Engineering	Head	Kento Doi

Central Supply Service	Head	Kazuhiko Fukatsu
Intensive Care Unit	Head	Naoto Morimura
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 Center	Head	Naoto Morimura
Department of Pain and Palliative Medicine	Head	Masahiko Sumitani
Children's Medical Center	Head	Naoto Takahashi
Department of Disaster Medical Management	Head	Naoto Morimura
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.

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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

Project Research Associate

Akihisa Tsutsumi, 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, Koichiro Yamashita, Yuma Tani, and Yuqing Liue (graduate students), Yuta Komori, and Ueno Risa (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.

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Department of Cytoarchitectonics

Lecturer

Yosuke Tanaka, M. D.

Research Associate

Tadayuki Ogawa, Ph. D.

Home page <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, cryoelectron microscopy at atomic resolution, and cryoultramicrotomy, biochemistry, immunocyto-

chemistry, 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.

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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 26 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

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and MENTAL20) Health Initiative: A Global Consortium Addressing the Human and Economic Burden of Brain, Spine, and Mental Disorders Through Neurotech Innovations and Policies *Journal of Alzheimer's Disease* 2021 Sep 3. doi: 10.3233/JAD-215190.

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.

Project Associate Professor

Chieko Saito, Ph.D.

Project Lecturer

Ikuko Koyama-Honda, Ph.D.

Project Research Associate

Junichi Sakamaki, Ph.D., Takeshi Sugawara, Ph.D., Seiichi Koike, Ph.D. (~Apr 2020),
Tomoya Eguchi, M.D., Ph.D.

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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 then took up a professorship at Tokushima University School of Medicine. In 1982, he succeeded Professor Yamakawa. He studied ribosomal RNA and cloned interferon and p450 genes.

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

Professor Noboru Mizushima graduated from Tokyo Medical and Dental University, Faculty of Medicine in 1991. After receiving Ph.D., he studied at National Institute for Basic Biology in Okazaki and started works on autophagy in yeast and mammals at Dr. Yoshinori Ohsumi's laboratory. Taking a position as a PI at the Tokyo Metropolitan Institute of Medical

Science in 2004, he started studies on 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.

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 allow 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 2020, we reported the following novel findings.

The formation of autophagosomes is a phenomenon that involves a unique, dynamic change in membrane morphology. Flattened disc-like vesicles bend into cup-shape structures and finally form spherical autophagosomes. Although many autophagy-related factors are involved in the formation of autophagosomes, the physical mechanisms behind the morphological changes have not been fully elucidated. We developed a mathematical model of the development of autophagosomes by the curvature generators, and analyzed the morphological changes during autophagosome formation. We showed that the spontaneous change in the distribution of curvature generators on the membrane determines the morphology of the

autophagic membrane. This mathematical model was able to quantitatively explain the autophagosome formation observed in live cells. These results suggest that a mathematical model based on simple physical mechanisms is effective in analyzing the seemingly complex membrane dynamics of autophagy (Sakai et al. *iScience* 2020).

We also reported, in collaboration with Dr. Otomo and colleagues at the Scripps Research Institute in USA, that mammalian ATG9 has scramblase activity and that the size of autophagosomes is significantly reduced in cells expressing functionally impaired ATG9 mutants that were created based on structural analysis (Maeda et al. *Nat Struct Mol Biol* 2020).

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 2020, we revealed a new physiological role for autophagy other than degradation. The lungs of mammals and the swimbladder of fish are air-containing organs that are essential for breathing and generating buoyancy in water, respectively. In order to inflate these organs with air, it is important to reduce the surface tension of the water that covers the epithelial cells of the alveoli and the swimbladder. This is done by a lipid-rich substance called a surfactant, which spreads on the surface of the water at the air-water interface. These surfactants are produced and stored in the lysosome-related organelle, lamellar body. In this study, we have shown that autophagy is required for the generation of the surfactants in lungs and swimbladders by analysis using mice and zebrafish. In the epithelial cells of lungs and swimbladders, autophagosomes fuse with immature lamellar bodies occurs, and suppression of autophagy results in insufficient maturation of

lamellar bodies. Such mice become lethal immediately after birth due to respiratory distress, and zebrafish are unable to maintain a floating posture in the water. Autophagy may contribute to lamellar body maturation by supplying lipid components (membranous organelles and autophagosome inner membrane) to lamellar bodies and/or expanding the surface area of lamellar body membranes (Morishita et al. *Cell Rep* 2020).

3. Methods for monitoring autophagic activity

Measuring autophagic activity is critical to dissect 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.

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

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Department of Cellular Signaling

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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, since August 2018. 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 A₂ (PLA₂) family, we aim to elucidate the molecular pathophysiology of diseases (*e.g.* metabolic and immune diseases) that are problematic in modern society. Based on this, we will promote the research of Quality of Lipids (QOL) for Quality of Life (QOL) and aim at building a theoretical foundation for diagnosis, prevention and treatment of diseases involving alteration of lipid metabolism.

1) Metabolic diseases

We previously reported that PLA2G5 (sPLA₂-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 (sPLA₂-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 sPLA₂-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 (iPLA₂γ), which acts as PLA₁/A₂, 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 (sPLA₂-IIF), which is specifically expressed in epidermal keratinocytes, mobilizes lysoplasmalogen, a unique lysophospholipid that promotes epidermal hyperplastic diseases such as psoriasis and skin cancer (Yamamoto et al, *J Exp Med*, 2015), and that PNPLA1, a member of the intracellular iPLA₂ 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). Furthermore, by phenotypic screening (with perturbation of skin barrier function as a readout) using a series of PLA₂ knockout strains, as well as by gene expression profiling of PLA₂-related genes in mouse and human skins, we have identified several PLA₂s that appear to be linked to the regulation of skin homeostasis and diseases.

Among these PLA₂s, PLA2G4E (cPLA₂ε), 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.

PLA2G3 (sPLA₂-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, *Pla2g3*^{-/-} mice display more severe atopic

dermatitis-like symptoms with increased expression of type 2 cytokines and chemokines (IL-4, IL-13, IL-33, TSLP, and CCL17), serum IgE levels, eosinophil infiltration, and scratching behavior. Global or skin-specific deletion of EP4 (PGE₂ receptor) or FP (PGF_{2α} receptor) largely if not solely recapitulate these phenotypes, suggesting that the PLA2G3-driven PGE₂-EP4/PGF_{2α}-FP signaling in keratinocytes plays an important role in skin barrier formation and thereby skin homeostasis, perturbation of which leads to exacerbation of atopic dermatitis.

3) Allergic and other immunological diseases

We previously reported that PLA2G3, an sPLA₂ isoform secreted from mast cells (MCs), promotes MC maturation by driving the paracrine PGD₂ circuit in cooperation with microenvironmental fibroblasts (Taketomi et al, *Nat Immunol* 2013) and that PAF-AH2, a unique PLA₂ that hydrolyzes oxidized phospholipids, ensures optimal MC activation and thereby allergic responses through producing unique EPA/DHA metabolites (ω3 epoxides) (Shimamaka et al, *Nat Med* 2017). We have recently confirmed the role of PLA2G3 in MCs by demonstrating that mice lacking PLA2G3 specifically in MCs, like those lacking the enzyme in all tissues, have immature MCs and display reduced local and systemic anaphylactic responses. In addition, MC-specific *Pla2g3*-null mice display an aggravated contact hypersensitivity (CHS), which is phenocopied by MC-specific deletion of hematopoietic PGD₂ synthase. Thus, MC-secreted PLA2G3 promotes MC maturation via PGD₂, thereby facilitating acute anaphylactic reaction and limiting delayed CHS response (Taketomi et al, *Cells* 2021). Furthermore, we have recently found that PLA2G3 is also coupled with an additional lipid mediator, lysophosphatidic acid (LPA), which acts in concert with PGD₂ to facilitate MC maturation.

PLA₂ subtypes that regulate T cell immunity are unknown. By transcriptional and functional screening of PLA₂ enzymes expressed in T cells, we have found that PLA2G12A (sPLA₂-XIIA), an orphan sPLA₂, 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) Cancer

Despite the restricted intestinal expression of PLA2G2A (sPLA₂-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. These results highlight a new aspect of PLA2G2A as a modulator of gut microbiota, perturbation of which affects distal skin responses (Miki et al, *JCI Insight*, in press).

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 sPLA₂-driven lipid metabolism. Hydrolysis of EV phospholipids by PLA2G10 (sPLA₂-X), which is induced in macrophages of Epstein-Barr virus (EBV) lymphoma, increases the production of fatty acids, lysophospholipids and their metabolites. sPLA₂-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 sPLA₂ inhibitor, while treating the mice with sPLA₂-modified EVs can reverse this phenotype. Overall, the sPLA₂-driven EV modification promotes tumor development (submitted).

5) Infectious diseases

PLA2G2D expressed in dendritic cells and M2 macrophages attenuates anti-viral Th1 immunity by supplying ω3 PUFAs and PGD₂. In collaboration with a foreign group, we have reported that *Pla2g2d* deficiency protects mice from pneumonia caused by coronavirus infection (Vijay et al, *J Exp Med* 2015; Zheng et al, *J Clin Invest* 2021; Roy Wong et al, *bioRxiv* 2021). Therefore, PLA2G2D may be an attractive drug target for treatment of COVID-19.

6) Neuronal diseases

Mutations in the *PNPLA6* gene cause neuronal and

retinal degeneration such as hereditary spastic paraplegia (SPG39), Boucher-Neuhauser syndrome, Oliver-McFarlane syndrome, and Laurence-Moon syndrome. However, it is unclear how *PNPLA6* mutations lead to these disorders. We have confirmed that PNPLA6 acts a phospholipase B (PLA₁/A₂ + 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. 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.

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).

Publications

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Department of Physiological Chemistry and Metabolism

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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, 1 postdoctoral fellow, 6 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, $Dlx5/Dlx6$ -independent mechanisms, whereas ET-1/ETAR signaling is involved in ventral identification of the pharyngeal arches through $G_{q/11}$ -mediated, $Dlx5/Dlx6$ -dependent 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.

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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 three 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 across the plasma membrane, which regulate various physiological processes. 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 approximately 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 two years, our results comprise more than 30 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 last year 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.

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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) Sensory inputs sparsely activate neurons in the sensory cortex, which is postulated to be an efficient information coding. However, how sparsely active neurons represent information and how the information is optimally decoded from the sparse representation have not been determined.

In the primary visual cortex (V1), simple cells each have a receptive field (RF) structure that is modeled by a two-dimensional (2D) Gabor function. Theoretically, a single natural scene is represented by a relatively small number of neurons using Gabor-like

RFs, whereas information about multiple scenes is distributed among the neuronal population. Indeed, V1 neurons sparsely respond to natural scenes. Population activity with higher sparseness exhibits greater discriminability between natural scenes.

What types of information from natural scenes are represented in the sparsely active neurons in the brain? The visual contents of natural scenes are reconstructed from single-unit activity within the lateral geniculate nucleus collected from several experiments and functional magnetic resonance imaging data from the visual cortices. However, whether the visual contents of natural images could be represented by simultaneously recorded, sparsely active neurons has not been addressed experimentally. It also remains to be revealed which decoding strategy is the most optimal for sparse representation. Whether only the small number of strongly active neurons represent information, or whether the remaining neurons contribute additional information remains to be determined. Furthermore, do the sparsely active neurons reliably represent the natural image contents, regardless of trial-to-trial response variability? Although a computational model has suggested that sparse and overcomplete representation is optimal for natural image representation with unreliable neurons, this model has not been examined experimentally.

We also address how visual information is distributed in a neuronal population. Some neurons are “unresponsive” to simple visual stimuli, such as moving gratings (e.g., the response rate of the mouse V1 is 26–68%). However, this may be partly because visual stimuli are not complex enough to completely cover the RF properties of all neurons. The proportion of neurons involved in the information processing is a matter of debate.

Here, we examined how sparsely active neurons represent natural image contents and how the information was optimally decoded from this sparse representation. Using two-photon calcium (Ca^{2+}) imaging, we recorded visual responses to natural images from the V1 of anesthetized and passively viewing awake mice. A small percentage of neurons responded to each image, which was sparser than that predicted by a linear encoding model. On the other hand, most neurons were involved in processing of natural images. The visual contents of a natural image

were linearly decodable from a small number of highly responsive neurons, and the additional use of the remaining neurons even degraded the reconstruction performance. The responsive neurons reliably represent the image, regardless of trial-to-trial response variability, which was supported by multiple neurons with partially overlapping representation. These results revealed a new representation of a natural image by a small number of neurons in which information is reliably represented, while the corresponding neuronal patterns change across trials and implies that collecting only the activity of highly responsive neurons is an optimal decoding strategy for sparse representation. (Hayashi et al., 2018).

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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, 2 postdoctoral researchers, 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) Structural dynamics and stability of corticocortical and thalamocortical axon terminals during motor learning

Synapses consist of presynaptic and postsynaptic sites, and are indispensable prerequisites for communication between neurons. Anatomically, synapses can be newly formed, eliminated, or undergo a change in size. Motor learning induces synaptic plasticity in M1. *In*

vivo two-photon imaging in rodents revealed that dendritic spines in M1 dynamically change during motor learning, and that the stabilization of a subset of L1 spines of layer 5 (L5) pyramidal neurons, which are newly formed in the early stage of learning, is relevant to improvement in motor performance. However, the structural plasticity of axonal boutons in M1 during motor learning is poorly understood. L1 dendritic spines in M1 receive not only axons from M1 neurons, but also axons from neurons in the secondary motor cortex (M2) and motor thalamus, with M2 and the motor thalamus being necessary for motor skill learning. Therefore, we hypothesized that the M2–M1 and thalamocortical pathways have distinct roles in motor learning, and that their axonal boutons would show distinct structural plasticity.

First, we anatomically confirmed that L1 in M1 receives axonal projections from M2 and the thalamus. Next, we injected adeno-associated virus (AAV) encoding either the tdTomato gene or GFP into M2 or the motor thalamus. After 2–3 weeks, we used two-photon microscopy to image the fluorescently labeled axons and their *en passant* boutons in L1 of M1 in anesthetized mice. The bouton size was larger in thalamic boutons than in M2 boutons. This result is consistent with previous studies showing that thalamocortical synapses are larger than corticocortical synapses. Over a 7-day training period, a group of mice were trained to perform an accelerating rotarod task with the rotation speed being increased from 3 to 100 RPM over 3 min. We pursued the axonal boutons in the same imaging fields under anesthesia on days 0, 2, 4, and 7 in both the trained mice and untrained control mice. We found that the total numbers of M2 and thalamic boutons were similar between the trained and control mice across the imaging days. In the trained mice, the relative size of thalamic boutons on day 2 in comparison with their size on day 0 was slightly larger than in the control mice. The sizes of thalamic boutons on day 7 and M2 boutons on days 2–7 were similar between the trained and control mice.

Next, we examined the stability and dynamics of M2 axonal boutons during learning. The survival rate of M2 boutons that existed on day 0 in both trained and control mice (pre-existing boutons) showed a gradual decrease over time. The day 7 survival rates of

pre-existing M2 boutons in trained and control mice were approximately 85%. In both trained and control mice, the day 0 sizes of those pre-existing M2 boutons that were still present on day 7 were larger than those that were eliminated before day 7. Thus, large boutons were more stable than small boutons.

When the formation, elimination, and turnover rates were averaged over days 0–2, 2–4, and 4–7, the formation rates of M2 boutons were higher in trained mice than in control mice. When the formation and elimination rates for each interval between imaging days were compared between the control and trained mice, only the formation rate during days 2–4 was significantly higher in trained mice than in control mice. These results suggest that formation of M2 boutons generally increased during the training days. The survival rates of boutons that were newly formed over days 0–2 or 2–4 were similar between trained and control mice.

In contrast to M2 axonal boutons, the day 7 survival rate of pre-existing thalamic boutons was higher in trained mice than in control mice, exceeding 0.9. Consistent with the M2 dynamics, the day 0 sizes of those pre-existing thalamic boutons that were still present on day 7 were larger than those that were eliminated before day 7. By contrast, the day 7 survival rate of small pre-existing thalamic boutons was higher in trained mice than in control mice. These results suggest that some of the pre-existing thalamic boutons stabilized during motor learning. In contrast to M2 axonal boutons, the training-period-averaged elimination rate of thalamic boutons was significantly lower in trained mice than in control mice, as was the elimination rate over days 4–7. These results suggest that the elimination of thalamic boutons generally decreased over the training days. Our results suggest that the late stabilization of thalamic boutons in M1 contributes to motor skill learning.

(2) Reorganization of cortical activity during learning of a forelimb motor task in the marmoset

It is indispensable to unravel information processing mechanism under physical movement for development of functional recovery after intracranial injury, auxiliomotor robot and so on. Previous studies of motor learning on the non-human primate have mainly employed macaque monkeys. However, it is very

difficult to record several areas simultaneously or track the same subsets of neurons over the long term with calcium imaging that is well used in rodent studies.

Instead, we use common marmoset (*Callithrix jacchus*), a New-World monkey, to visualize the neuronal activity by introducing a fluorescent protein in the cerebral cortex to elucidate the reorganization during motor learning. Although the brain of marmoset is approximately 10-fold smaller than that of macaque, it is known that its basic cytoarchitecture is common with those of other primates including the human. Furthermore, its lissencephalic form is suitable for calcium imaging with fluorescent proteins.

In the behavior task, we train marmosets to control a pole with the left forelimb to move a cursor to a target on the monitor to acquire a reward. First, the animals learned a pole-pull task. Then, we injected AAV coding GCaMP into M1, the premotor area (PM), and the surrounding areas. After GCaMP expression became substantially high, we introduced a pole-push task to the motor task. Performing the task for 30-90 minutes per day, the animals learned the novel movement, the movement of the forelimb pushing the pole, in 20-40 days. To clarify whether the movement-direction selectivity of neuronal activity changes during movement learning or not, we conducted one-photon imaging for simultaneous multiarea recording and two-photon imaging for tracking layer 2/3 neurons in M1 and PM throughout the motor learning period. We are now analyzing the neuronal encoding and decoding of physical movements with neuronal activity recorded with calcium imaging and physical movements extracted with CCD camera and deep learning algorithm. Additionally, we examine whether inhibition of the neuronal activity in task-related M1 and PM with microinjection of muscimol.

As mentioned above, employing not only classical physiological method but novel genetic engineering techniques and mathematical and statistical methods as well onto marmosets, we have deepened our understanding of the neural mechanisms of motor learning as never before. We expect that our study will contribute to both basic and clinical medicine because the results may be applied to the human.

(3) Independent representations of reward-predicting cues and reward history in frontal cortical neurons

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.

In the rodent cerebral cortex, M2 plays critical roles in value estimation, action selection, working memory, and motor planning. The type of action required to obtain a reward varies across different decision-making studies, and the representation of each M2 neuron is frequently assigned to one type of task-related information, that which is dominantly represented.

To clarify action-type-independent decision-making-related information in M2, 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). We found that in all dorsal cortical areas, licking-related activity dominated, while information regarding the reward-predicting cue emerged over the dorsal cortex and information regarding the recent reward history emerged in the

frontal cortex. Individual dmFrC neurons strongly but separately represented these types of task-related information. Our results suggest that dmFrC can integrate different types of task-related information to select the appropriate action in the decision-making process.

(From a paper submitted to Biorxiv in 2020)

(4) Non-action Learning: Saving action-associated cost serves as a covert reward

“To do or not to do” is a fundamental decision that has to be made in daily life. Behaviors related to multiple “to do” choice tasks have long been explained by reinforcement learning, and “to do or not to do” tasks such as the go/no-go task have also been recently discussed within the framework of reinforcement learning. In this learning framework, alternative actions and/or the non-action to take are determined by evaluating explicitly given (overt) reward and punishment. However, we assume that there are real life cases in which an action/non-action is repeated, even though there is no obvious reward or punishment, because implicitly given outcomes such as saving physical energy and regret (we refer to this as “covert reward”) can affect the decision-making. If this is the case, can learning of the non-action be explained by an increase in the value of the non-action according to such a covert reward? If not, is the non-action chosen because of the reduction in the action value?

To address these issues, we developed a new behavioral paradigm in which head-fixed mice choose to either pull a lever with their right forelimb. In the current task, mice chose to pull a lever or not according to two tone cues assigned with different water reward probabilities (70% and 30% in condition 1, and 30% and 10% in condition 2). As the mice learned, the probability that they would choose to pull the lever decreased (<25%) in trials with a 30% reward probability cue (30% cue) in condition 1, and in trials with a 10% cue in condition 2, but increased (>80%) in trials with a 70% cue in condition 1 and a 30% cue in condition 2, even though a non-pull was followed by neither an overt reward nor avoidance of overt punishment in any trial.

This behavioral tendency was not well explained by a combination of commonly used Q-learning models, which take only the action choice with an overt

reward outcome into account. Instead, we found that the non-action preference of the mice was best explained by Q-learning models, which regarded the non-action as the other choice, and updated non-action values with a covert reward. We propose that “doing nothing” can be actively chosen as an alternative to “doing something,” and that a covert reward could serve as a reinforcer of “doing nothing.”

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Introduction and Organization

This laboratory was founded in 1953 as Department of Neurophysiology, Institute for Brain Research. In 1996, it was integrated into Graduate School of Medicine. The current members of this laboratory are 4 faculty members (professor, lecturer, 2 research associate), 1 postdoctoral fellows, 9 graduate students, 2 research student and 6 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 gastricne-mius 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 culture, 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 trans-

mission 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.

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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.

Pharmacol. Sci., 144, 83-88 (2020)

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

Recently, nanoscale molecular distribution in synapses is suggested to be a key determinant of synaptic function. To reveal the relationship between the nanoscale molecular assemblies and synaptic functions, we are trying to perform a super resolution microscopic analysis in combination with glutamate imaging. These advanced imaging technique 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.

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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 species shows characteristic different sleep duration. However, detailed molecular mechanisms underlying the control of sleep duration in mammals are still elusive. Using triple-target CRISPR, SSS, and CUBIC techniques together with a computational model that simulates the membrane potential of cortex neuron regulated by a group of ion channels, we have discovered and proposed that Ca^{2+} -dependent neuronal hyperpolarization pathway affects sleep duration in mammals (Sunagawa et al., Cell Reports 2016; Tatsuki et al., Neuron 2016; Yoshida et al. PNAS 2019).

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 $\text{CaMKII}\alpha/\beta$ 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 (posttranslational modification of intracellular signaling pathways). 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 also 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.

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Pathology, Immunology and Microbiology

1. Pathology

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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 Division of Diagnostic 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. Miyama moved to Saitama Medical University International Medical Center. Dr. Domoto moved to Nippon medical school hospital. Dr. Tateishi became a lecture of the department and Dr. Iwasaki became an associate of the department.

Dr. Shinozaki-Ushiku became an associate professor of Division of Integrative Genomics on June

1st, 2020, and Dr. Tanaka become a lecturer on February 1st, 2021.

Five postgraduate students (Kume, Fukazawa, Furuya, Hoshi, and Yasunaga) finished the course and received Ph.D. In the new fiscal year, 2021, six new students will enter the postgraduate course, and there will be 22 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. For the four years since FY2018, in graduate school education, we plan to train pathologists, who are specialized in "death investigation, remote pathology diagnosis, and genomic medicine" with the training system oriented to region support by making them rotate among universities.

Teaching activities

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

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. Concerning the exercises of Systemic Pathology Course, we have established a web system to access whole slide imaging by which students can look at pathology slides online.

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. 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 Saito), Epstein-Barr virus-associated neoplasms (Drs. Shinozaki-Ushiku, Abe and Hinata), pancreatobiliary tumors (Drs. Tanaka and Yamauchi), bone and soft tissue tumors (Dr. Makise). 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).

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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. In March 2021, the Department consists of a professor, two associate professors, three assistant professors, technical assistants, and some research fellows, including four graduate students, a master course student, and two post-doctoral fellows.

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. Teaching responsibilities include lectures on General Pathology related to the mechanisms of diseases. Since we believe it very important for medical students to study basic oncology, we teach a basic tumor biology course 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” twice a month and “Monday Seminar” once a month. We have been doing collaboration 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 some of our graduate students are supported by this program. This program will stimulate interaction between students and scientists in the programs as well as those from other laboratories (square.umin.ac.jp/wings-lf/).

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).

Followings are some research results obtained at our laboratory in 2020.

1) *Epigenetic remodeling shapes inflammatory renal cancer and neutrophil-dependent metastasis*

Advanced clear cell renal cell carcinoma (ccRCC) often causes systemic inflammatory responses. Cancer cells reshape the immune landscape by secreting various cytokines or chemokines. This phenotype, known as cancer-cell-intrinsic inflammation, triggers a metastatic cascade. By multiple cycles of orthotopic transplantation of human ccRCC cells into the mouse kidney and establishment of highly malignant ccRCC sublines, we investigated the functional roles and regulatory mechanisms of inflammation driven by the highly malignant ccRCC cells. The inflammatory responses of advanced ccRCC were recapitulated in the highly malignant ccRCC. Amplification of cancer-cell-intrinsic inflammation during ccRCC progression triggered neutrophil-dependent lung metastasis. Massive expression of inflammation-related genes was transcriptionally activated by epigenetic remodeling through mechanisms such as DNA demethylation and super-enhancer formation. A bromodomain and extra-terminal motif (BET) inhibitor synchronously suppressed C-X-C-type chemokines in the highly malignant ccRCC cells and decreased neutrophil-dependent lung metastasis. These findings demonstrate the nature of inflammatory ccRCC, which triggers metastatic cascades, and suggest a potential therapeutic strategy for advanced ccRCC (Nishida et al. Nat Cell Biol 2020).

2) *NTSR1 (neurotensin receptor 1) signaling promotes pancreatic cancer progression*

Pancreatic cancer is one of the cancers with the poorest prognosis, with a 5-year survival rate of approximately 5-10%. Using multiple cycles of transplantations in a mouse pancreatic orthotopic inoculation model, we previously generated highly malignant pancreatic cancer sublines with increased tumor-forming abilities in vivo. Using these cells, we

screened potential molecular targets for the treatment of pancreatic cancer. Among the genes with increased expression levels in the pancreatic cancer sublines, we picked up the genes encoding cell surface receptors that may play important roles in the interactions between cancer cells and the tumor microenvironment. By searching our previous RNA-sequence analysis data, we found increased expression levels of NTSR1 in highly malignant pancreatic cancer sublines. Analysis of clinical databases showed that the expression level of NTSR1 was increased in advanced pancreatic cancer. Moreover, high NTSR1 levels were correlated with a poor prognosis. Overexpression of NTSR1 in human pancreatic cancer cells accelerated the tumorigenic and metastatic abilities in vivo. RNA-sequence analysis showed that MAPK and NF- κ B signaling pathways were activated upon neurotensin stimulation in highly malignant cancer sublines. Neurotensin stimulation increased the expression of MMP-9 and other pro-inflammatory cytokines and chemokines in pancreatic cancer cells. Furthermore, treatment with SR48692, an NTSR1 antagonist, suppressed the activation of the MAPK and NF- κ B signaling pathways and induction of target genes in pancreatic cancer cells in vitro, and the administration of SR48692 suppressed the tumorigenicity of pancreatic cancer cells in vivo. NTSR1 may thus be a prognostic marker and a molecular target for pancreatic cancer treatment (Takahashi et al. Mol Oncol 2020).

3) *Whole-organ analysis of TGF- β -mediated remodeling of the tumor microenvironment by tissue clearing*

Tissue clearing is one of the most powerful strategies for a comprehensive analysis of disease progression. We established an integrated pipeline that combines tissue clearing, 3D imaging, and machine learning. This pipeline provided the spatial information of the tumor microenvironment. We explored the role of TGF- β in cancer metastasis using human lung adenocarcinoma A549 cells. TGF- β -stimulated cancer cells enhanced metastatic colonization of unstimulated-cancer cells in vivo when these cells were mixed. RNA-sequencing analysis showed that expression of the genes related to blood coagulation and inflammation were up-regulated in TGF- β -stimulated cancer cells. Further, whole-organ analysis

showed the accumulation of platelets or macrophages with TGF- β -stimulated cancer cells, suggesting that TGF- β might remodel the tumor microenvironment, enhancing the metastatic colonization of cancer cells. Our integrated pipeline for 3D profiling will help the understanding of the tumor microenvironment during the process of cancer metastasis (Kubota et al. Commun Biol 2020).

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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. Takahashi 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 biotechnology
- 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, 50,000 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 oncoprotein interacts with SHIP2 to increase its delivery into gastric epithelial cells

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. 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 undergoes tyrosine phosphorylation by Src family kinases (SFKs) or c-Abl kinase at the Glu-Pro-Ile-Tyr-Ala (EPIYA) motif. Tyrosine-phosphorylated CagA acquires the ability to specifically bind to and aberrantly activate SHP2 tyrosine phosphatase, causing aberrant activation of the RAS-ERK MAP kinase signaling pathway. SHP2 has been recognized as a pro-oncogenic phosphatase and activating mutations of SHP2 have been found in a variety of human malignancies.

The EPIYA motif-containing region of individual CagA consists of various combinations of 4 distinct segments (termed EPIYA-A, EPIYA-B, EPIYA-C, and EPIYA-D), each of which is defined by differences in the amino acid sequences surrounding the EPIYA motif. *H. pylori* strains isolated in East Asian countries comprise EPIYA-A, EPIYA-B, and EPIYA-D segments (East Asian CagA). In contrast, *H. pylori* strains isolated all over the world except East Asian countries comprise EPIYA-A, EPIYA-B, and EPIYA-C segments (Western CagA). CagA binds to SHP2 through tyrosine-phosphorylated EPIYA-C or EPIYA-D segments. Notably, SHP2 binds to EPIYA-D with 2 order of magnitude stronger affinity than to EPIYA-C.

In this study, we found that SHIP2, an SH2 domain-containing phosphatidylinositol 5'-phosphatase, is a hitherto undiscovered CagA-binding host protein. Similar to SHP2, SHIP2 binds to the Western CagA-specific EPIYA-C segment or East Asian CagA-specific EPIYA-D segment through the SH2 domain in a tyrosine phosphorylation-dependent manner. In contrast to the case of SHP2, however, SHIP2 binds more strongly to EPIYA-C than to EPIYA-D. Interaction with CagA tethers SHIP2 to the plasma membrane, where it mediates production of phosphatidylinositol 3,4-diphosphate [PI(3,4)P₂]. The CagA-SHIP2 interaction also potentiates the morphogenetic activity of CagA, which is caused by CagA-deregulated SHP2. This study indicates that initially delivered CagA interacts with SHIP2 and thereby strengthens *H. pylori*-host cell attachment by

altering membrane phosphatidylinositol compositions, which potentiates subsequent delivery of CagA that binds to and thereby deregulates the prooncogenic phosphatase SHP2. In addition, this study indicates that CagA-SHIP2 interaction plays an important role in quantitatively increasing the pathological activity of Western CagA, which is qualitatively less bioactive than East Asian CagA, by facilitating CagA delivery.

2. Alternative splicing reverses the cell-intrinsic and cell-extrinsic prooncogenic potentials of YAP1

YAP1 is a transcriptional co-activator that interacts with a number of transcription factors, most notably TEADs, and thereby transactivates downstream target genes, which stimulates cell proliferation while preventing cell death. YAP1 shuttles between the cytoplasm and nucleus in response to various signals including the Hippo signal, which plays an important role in restricting organ size by controlling cell proliferation and apoptosis. The Hippo pathway contains two core serine/threonine kinases: MST and LATS. When the Hippo signal is off, nonphosphorylated YAP1 enters the nucleus, where it acts as a transcriptional co-activator by binding with TEADs. When the Hippo signal is on, however, MST-activated LATS phosphorylates cytoplasmic YAP1 to prevent its nuclear translocation. Thus, impaired Hippo signaling also contributes to neoplastic transformation of cells by deregulating YAP1.

In addition to acting as a transcriptional co-activator, YAP1 directly mediates translocation of the pro-oncogenic phosphatase SHP2 from the cytoplasm to nucleus. In the cytoplasm, SHP2 potentiates RAS-ERK signaling, which promotes cell proliferation and cell motility, whereas in the nucleus, it mediates gene regulation. YAP1 comprises multiple splicing isoforms defined in part by the presence (as in YAP1-2 γ) or absence (as in YAP1-2 α) of a γ -segment encoded by exon 6 that disrupts a critical leucine zipper. Although the disruptive segment is known to reduce co-activator function, it is unclear how this element impacts the physical and functional relationships between YAP1 and SHP2.

To explore this question, we first demonstrated that YAP1-2 γ cannot bind SHP2. Nevertheless, YAP1-2 γ

exhibits stronger mitogenic and motogenic activities than does YAP1-2 α because the YAP1-2 α -mediated delivery of SHP2 to the nucleus weakens cytoplasmic RAS–ERK signaling. However, YAP1-2 γ confers less *in vivo* tumorigenicity than does YAP1-2 α by recruiting tumor-inhibitory macrophages. Mechanistically, YAP1-2 γ transactivates and the YAP1-2 α –SHP2 complex transrepresses the monocyte/macrophage chemoattractant *CCL2*. Thus, cell-intrinsic and cell-extrinsic pro-oncogenic YAP1 activities are inversely regulated by alternative splicing of exon 6. Notably, oncogenic KRAS down-regulates the SRSF3 splicing factor that prevents exon 6 skipping, thereby creating a YAP1-2 α -dominant situation that supports a “cold” immune microenvironment.

Publications

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Department of Infection Control and Prevention

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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 1, 1993 and the present department on June 4, 1994. Currently, our faculty consists of one professor, one lecturer, five research associates, 12 laboratory technicians, and two office assistants. For isolation and identification of microorganisms from clinical specimens, we amalgamated the microbiology unit from the Department of Clinical Laboratory in 2001.

Clinical activities

Our daily activities are as follows:

- 1) Surveillance and control of hospital-acquired infection, such as infection or colonization of methicillin-resistant *Staphylococcus aureus* and other drug-resistant microbes.

- 2) Investigation of trends in weekly bases and monthly reports to all departments; Screening of colonization; monitoring of appropriate use of antibiotics.
- 3) Microbiological investigation of wards and environment.
- 4) Detection, investigation, intervention and control of the hospital infection outbreak.
- 5) Offering of information and advice on HIV-infected patients' management.
- 6) Direct inquiries and advises on management of patients with various infections through ward rounds every week.

Education

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

education of graduate students as well as hospital staff.

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

Research

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 pneumoniae* infection

Publications

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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 $\gamma\delta$ T 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). 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.

We have reported that the genetic variations of human *PSMB11* gene, which encodes $\beta 5t$, a thymus-specific proteasome subunit, affected the MHC class I-bound peptide repertoire in the thymus and positive selection of CD8 T cells (Nitta et al., Sci Immunol., 2017). 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 $\gamma\delta$ T cells. We showed that the $\gamma\delta$ TCR signal mediated by the Syk-PI3K pathway is essential for thymic development of IL-17-producing $\gamma\delta$ T cells (Muro et al., J Clin Invest., 2018). These findings suggest that the Syk-PI3K pathway might be a therapeutic target of inflammatory diseases. Recently, we generated mutant mice lacking all of the Skint family genes (Skint1-11) that encode candidate thymic factors for regulation of $\gamma\delta$ T cell development (Narita et al., Int Immunol., 2018). These mice exhibited a marked reduction of V γ 5V δ 1 $\gamma\delta$ T cells in the thymus and skin, but had normal development of other $\gamma\delta$ T cell subsets and leukocytes. This study indicates an exclusive function of Skint family genes in the development of V γ 5V δ 1 $\gamma\delta$ T cells and provides a useful animal model to analyze the mechanism for thymic education of $\gamma\delta$ T 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 (γ_c) and JAK3, which are required for the development of iNKT cells and the proliferation and survival of peripheral T cells. PRMT5 induced the arginine methylation of the spliceosomal component SmD3 that promoted the splicing of pre-mRNA encoding γ_c and JAK3. In recent years, Jak inhibitors have attracted attention as potential agents for the autoimmune diseases such as rheumatoid arthritis. This study presented an entirely new regulatory mechanism governing γ_c family cytokine-Jak3 signaling in T cells (Inoue et al., *Nat Immunol.*, 2018).

3) Mechanism of autoimmune disease

The IL-17 producing helper T cell subset (Th17 cell) plays critical roles in several autoimmune disease

models such as collagen induced arthritis (CIA) and experimental encephalomyelitis (EAE). We have identified I κ B ζ as an indispensable transcription factor for Th17 cell differentiation (Okamoto et al., *Nature*, 2010). However, in both RA and EAE models, 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. These results show that the targeting these cells and/or molecules could be effective in preventing bone destruction in RA (Danks et al., *Ann Rheum Dis.*, 2016).

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 medullary thymic epithelial cells (mTECs) ectopically express a variety of tissue-restricted antigens (TRAs) and thereby TRA-reactive immature T cells are deleted. It has been known that 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.

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Radiology and Biomedical Engineering

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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.

Teaching activities

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 activities

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

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Eighty three English articles in total, including another 47, have been published from our department in 2020. Please refer to our homepage, <http://www.ut-radiology.umin.jp/publication/2020.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

1. Cell responses to hemodynamic forces

Our studies have demonstrated that ECs have functional responses to hemodynamic forces, shear

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

2. Hemodynamic force-mediated gene regulation

We have demonstrated that shear stress regulates endothelial gene expression transcriptionally and/or posttranscriptionally. Shear stress downregulates VCAM-1 gene transcription via the double AP-1 binding element (TGACTCA) in the promoter which functions as a shear stress-responsive element. Shear stress has also been shown to increase the expression level of granulocyte/macrophage-colony stimulating factor (GM-CSF) via mRNA stabilization. Differential display and DNA microarray analysis showed that around 600 known and unknown transcripts were up- or down-regulated in human umbilical vein ECs exposed to a shear stress. From these shear stress-responsive genes, a cDNA encoding an unknown G-protein coupled receptor was cloned. We showed that the transcription factor SP1 is involved in the shear stress-induced down-regulation of P2X4 (an ATP-gated cation channel) gene expression in ECs. We also revealed that endothelial genes are differentially regulated by laminar and turbulent shear stress. Laminar shear stress decreases the gene expression of urokinase plasminogen activator (uPA), which plays a role in fibrinolysis and vascular remodeling, via both GATA6-mediated down-regulation of gene transcription and an acceleration of mRNA degradation, while turbulent shear stress increases the

uPA gene expression through mRNA stabilization. We demonstrated that shear stress up-regulates the gene expression of plasminogen activator inhibitor-1 (PAI-1) through activation of transcription factors Sp-1 and Ets-1 in human hepatocytes. We developed a compliant tube-type flow-loading device that allows simultaneous application of physiological levels of shear stress and cyclic strain to cultured cells and observed that the response of endothelial genes to shear stress or cyclic strain depends on whether the two forces are applied separately or together.

3. Hemodynamic force-induced cell differentiation

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

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

and exposed to pulsatile shear stress and cyclic strain, was developed.

4. Mechanosensing and mechanotransduction

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

Our study revealed that cell surface ATP synthase localized in caveolae/lipid rafts are involved in the shear-stress-induced ATP release by ECs. Recently, we demonstrate that the cellular mitochondria play a critical role in this process. Cultured human pulmonary artery ECs were exposed to controlled levels of shear stress in a flow-loading device and the changes in the mitochondrial ATP levels were examined by real-time imaging using a fluorescence resonance energy transfer-based ATP biosensor. Immediately upon the exposure of the cells to flow, the mitochondrial ATP levels increased, which was both reversible and dependent on the shear stress intensity. Inhibitors of the mitochondrial electron transport chain and ATP synthase, as well as knockdown of caveolin-1, a major structural protein of

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

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

5. Shear stress-induced mitochondria oxidative phosphorylation

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

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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 hydrolases, 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).

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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 interdisciplinary 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.

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Division of Integrative Genomics

Professor

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Associate Professor

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

Organization

The division of Integrative Genomics was established in January 2020 to comprehensively promote genomic research both clinically and basically. The activity of this division is linked to the Department of Clinical Genomics and Genomic Research Support Center, and will be to 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 Geneprofiting 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”.

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Neuroscience

1. Basic Neuroscience

Department of Neuropathology

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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 ($A\beta$) ending at 40th or 42nd residues ($A\beta_{40}$ and $A\beta_{42}$, respectively),

Dr. Iwatsubo has performed a systematic immuno-histochemical studies on autopsied brain tissues from patients with AD, Down syndrome and familial AD, and demonstrated that $A\beta_{42}$, that most readily form amyloid fibrils in vitro, is the initially and predominantly deposited species in human cerebral β -amyloidosis (Iwatsubo et al. *Neuron* 1994, *Ann Neurol* 1995). Dr. Iwatsubo's group then established cellular models expressing mutant forms of presenilin (PS) genes linked to familial AD (FAD), and using their original highly-sensitive ELISA quantitation system, his group has clearly shown that an increase in the production of $A\beta_{42}$ is the pathogenic mechanism leading to FAD (Tomita et al. *Proc Natl Acad Sci USA*, 1997). These findings have provided a firm basis for the currently prevailing β -amyloid hypothesis. They then focused on the mechanisms of γ -secretase complex that cleaves the C terminus of $A\beta$, and set out to cell biological studies using RNA interference on the formation and function of the γ -secretase complex harboring PS as the catalytic center, associated with three additional membrane proteins. They demonstrated that 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 also shown by establishing in vitro γ -secretase assays that sulindac sulfide, a major non-steroidal anti-inflammatory drugs, directly acts on γ -secretase and selectively reduce A β 42-generating activities (Takahashi et al., J Biol Chem, 2003), providing important implications to the therapeutic strategies of AD by γ -secretase modulation. Recently, he has established a novel method for an efficient in vitro reconstitution of γ -secretase complex, paving the way towards the structural analysis of active γ -secretase (Hayashi et al. J Biol Chem, 2004), and using thus highly purified γ -secretase particles, they have partially unveiled the submolecular structure of this complex by single-particle EM analysis (Ogura et al. BBRC, 2006). Very recently, 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 A β deposits in AD brains and extended it to a contemporary molecular/cellular biology of PS, that proved to play a key role in "intramembrane proteolysis".

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

Using cortical Lewy bodies purified from postmortem brains of patients with dementia with Lewy bodies (DLB) by his original method (Iwatsubo et al. Am J Pathol 1996) as immunogens, Dr. Iwatsubo's group, in collaboration with Drs. Virginia Lee and John Trojanowski at Univ. Penn, performed an extensive immunochemical search for components of Lewy bodies. They have demonstrated by raising a specific monoclonal antibody that α -synuclein, that proved to be a product of pathogenic gene for familial form of Parkinson's disease, is one of the major constituent of Lewy bodies in sporadic Parkinson's disease and DLB (Baba et al. Am J Pathol 1998). His group then purified aggregated α -synuclein from DLB cortices using fine biochemical techniques, purified it

to near homogeneity, and demonstrated using mass spectrometry and specific antibodies that α -synuclein deposited in synucleinopathy lesions is highly phosphorylated at a specific serine residue (Fujiwara et al. Nature Cell Biol 2002). This finding led to a range of studies focusing on the role of synuclein phosphorylation in neurodegeneration. Also, the phospho-specific α -synuclein antibody is widely used as the most sensitive marker for α -synucleinopathy lesions, and has characterized a wide spectrum of α -synuclein pathologies in neurodegenerative disorders.

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

The major component of Alzheimer's amyloid plaques is A β , although there are a number of non-A β components that potentially affect fibrillization and degradation of amyloid deposits. Among these, there has been an enigmatic "missing piece" protein of molecular masses of 50/100 kDa. Dr. Iwatsubo's group raised a monoclonal antibody against amyloid fraction that recognizes this protein, and using this antibody as a probe, they conducted a thorough biochemical purification of these antigens and finally cloned a cDNA coding for the precursor of this protein. This protein turned out to be a novel class of membrane-bound collagen, which was named CLAC (collagen-like Alzheimer amyloid plaque component) and its precursor CLAC-P (Hashimoto et al. EMBO J 2002). This finding had an immense impact both on fields of AD research as well as on general biology as a first discovery of neuron-specific collagen harboring a unique membrane-spanning structure. CLAC has been highlighted as a protein that may affect fibrillization of A β and contribute to amyloid plaque formation. Indeed, he has recently shown that CLAC-positive senile plaques constitute a unique subset of plaques distinct from the classical, β -sheet-rich amyloid deposits, underscoring the pathobiological role of CLAC in amyloid formation, and that CLAC inhibits fibrillization of A β in vitro. Knockout mice studies have confirmed the role of CLAC in neuromuscular development (Tanaka et al. J Neurosci, 2014).

4. 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).

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Department of Neurochemistry

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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 University) in March 2001, and the departure of Associate Professor David Saffen to initially University of Minnesota and then to Ohio State University in August 2001, Associate Professor Haruhiko Bito was appointed as Head of Department since January 2003. The Department is located on the 6th floor, in the West

wing of the third building of the Medical School. The Department currently enrolls one professor, one lecturer, two assistant professors, four postdoctoral scholars, one technical staff, five 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/CaMKI γ) is most expressed in the central nucleus of the amygdala and in the ventral medial hypothalamus, while also being present at a much weaker amount in most central neurons. Biochemical and cell biological studies indicated a critical role for lipidification of this kinase to be properly sorted into specific lipid-restricted membrane microdomains. The function played by this lipidified, membrane-inserted CaMK in circuitry formation and maturation was scrutinized using RNA interference. Along with the identification of the critical lipid-modifying enzyme that controls lipid-anchoring of this kinase, we discovered a novel activity-regulated mechanism whereby CLICK-III/CaMKI γ is actively sorted into dendritic lipid rafts, where it specifically regulates Rac-mediated actin remodeling that is required for BDNF-stimulated dendritogenesis (Takemoto-Kimura et al., *Neuron*, 2007; Takemoto-Kimura et al. *Eur. J. Neurosci.* 2010). Similar studies in axonal growth also suggest the active contribution of CaMKK cascade in this process (Ageta-Ishihara et al., *J. Neurosci.* 2009; Takemoto-Kimura et al., *Eur. J. Neurosci.* 2010). Using a membrane-tethered genetically encoded calcium indicator, we successfully recorded spontaneous regenerative calcium transients (SRCaTs) in developing mouse excitatory cortical neurons and discovered that

L-type VGCCs play critical roles in neural development and corticogenesis (Kamijo et al., J. Neurosci. 2018).

How do these multiple Ca^{2+} -dependent signaling molecules process each pattern of intracellular Ca^{2+} dynamics to induce a cellular response? Recently, we have developed a method named dFOMA (dual FRET imaging with optical manipulation) to simultaneously measure activities of two distinct signaling molecules in living neurons. Applying originally developed FRET probes to dFOMA method enabled us to measure activities of CaMKII, calcineurin and Ca^{2+} , when a neuron received various frequencies of synaptic inputs. These experiments provided evidence that CaMKII α and calcineurin are fine-tuned to unique bandwidths and compute input variables in an asymmetric manner (Fujii et al., Cell Reports 2013).

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-1 α released from the pia mater was likely to be a predominant Rho activator via stimulation of a cognate and specific GPCR CXCR4 (Arakawa et al., *J. Cell Biol.*, 2003). While a true gradient in SDF-1 α still remains to be demonstrated in vivo, it is intriguing to note that most active axonal process formation and elongation actually occur in the inner zone of EGL that is opposite and most distant from the interface with the pia mater (Bito, *J. Biochem.*, 2003). Most strikingly, we demonstrated that axon elongation could actively occur in an intermediate Rho activity range that enables ROCK to be weakened enough while allowing another Rho effector 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).

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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 2020, we had 6 graduate students. 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 2020 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

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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).

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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 (Memory Clinic).

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 Neuropathology,

consultation for Neurology, rotation at ER 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 test of a novel antisense nucleic acid 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.)

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. (Toda, T., Satake, W., Uenaka, T., Cha, P.C., Fujino, G.)

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. After identifying expanded intronic TTTCA and TTTTA repeats in three independent genes in patients with benign adult familial myoclonic epilepsy, which postulated a new disease mechanism in epilepsy, we also identified expanded CGG repeats in three genes are causes of neuronal intranuclear inclusion disease, oculopharyngeal myopathy with leukoencephalopathy, and oculopharyngodistal myopathy. We reported safety and efficacy of hematopoietic stem cell transplantation for adolescent-/adulthood-onset cerebral form/cerebello-brainstem form of 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.)

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 especially interested in plasticity induction by non-invasive brain stimulation (NIBS) techniques, offering potential for

clinical application. Our lab has a long experience in the use of transcranial magnetic stimulation (TMS) which is able to stimulate neurons in intact human brain and has devised a highly effective repetitive TMS method to induce long-term effects (quadripulse stimulation, QPS). We have recently started a clinical trial of repetitive TMS to treat patients with Parkinson's disease. (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 paraneoplastic 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 chronic 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. 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. We also developed a novel preanalytical sample handling protocol for high sensitivity measurement. We are also participating in observational studies of preclinical Alzheimer's disease (AMED Preclinical research) and DIAN-J studies.

(Atsushi Iwata, Yu Nagashima, Toji Miyagawa, 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)

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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, 2 lecturers, 2 project lectures, and 8 associates.

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 2021, 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 thromboembolic 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 intra-operative 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 disease, *NF2* in meningioma and schwannoma, *CCM* in cerebral cavernous malformation were analyzed. In addition, comprehensive genetic analyses, including analysis of whole exome sequences, were performed to

identify novel disease-related genes..

In the field of cerebrovascular disease, analysis of the *RNF213* gene revealed that *RNF213* variant is associated with not only moyamoya disease but also various intracranial artery stenosis. Furthermore, genome wide association study of intracranial artery stenosis was performed, and disease related gene polymorphisms were clarified. In addition, we have identified disease-related gene in venous malformations that occur in the head and conducting functional analysis.

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

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 analysing 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 comprehensive 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.

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.

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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, 10 technical assistants, 1 collaboration researcher, 1 academic support staff, and 1 assistant clerk. 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 fourth-year undergraduate students, and “Introduction to Preventive Medicine” in medical science master’s program. 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. Also, we are applying the obtained immune repertoire data to design antibodies and use them in cancer

treatment and prevention.

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 and showed that its mutation signature differs from the intestinal-type gastric adenocarcinoma, suggesting that carcinogenic factors are different in these two types of cancer. We are looking at cancer tissues as a whole, 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

histopathological 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. Our current focus is 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

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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, 4 project researchers (part-time), 2 supporting staff members, 9 graduate students (3 in PhD program, 6 in professional degree course), 16 part-time lecturers, and 36 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). Each group conducts field practice, review work, or laboratory work, and writes a report in the style of original or review paper. However, because of the COVID-19 pandemic, the above groups were reorganized into eight groups and the practice and work was conducted online.

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.

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

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

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

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

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

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

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

Postmortem examination

The determination of precise cause of death is one of the most important practices at our department. We perform medico-legal autopsies for around 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) started. 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 last year, it has become possible to accept SARS-CoV-2-infected bodies. While all cases were tested by the Department of Infection Control and Prevention of the University of Tokyo Hospital at the beginning of the pandemic, now that we have newly introduced our own real-time PCR system in our laboratory, conducting a SARS-CoV-2 PCR test in all cases.

Education

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

The lectures consist of forensic pathology, clinical forensic medicine, forensic toxicology, forensic radiology, forensic odontology and forensic genetics. In the Free Quarter training course, students experience laboratory practices (toxicology, 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 Health Science, and master course of Medical Science.

Research

In cooperation with other universities including Chiba University and Tokyo Medical and Dental University, researches in 6 sections (forensic pathology, clinical forensic medicine, forensic toxicology, forensic radiology, forensic odontology and forensic genetics) have proceeded.

1. Forensic Pathology

In autopsy, it is difficult to examine a vertebral artery. We therefore conduct study on a method of the artery using angioscopy. We also conduct research about the usefulness of coronary angiography using 3D-CT. As to pathological research, we investigate about the lipid peroxidation in the cases of stimulant intoxication and crash syndrome.

2. Clinical Forensic Medicine

We have started to liaise with child consultation centers to examine children suspected of suffering abuse. We will also collaborate with other institutions to establish a framework for child abuse examinations in Chiba Prefecture. Through these activities, we will continue to work to establish the practice of clinical forensic medicine while educating students and conducting research on the prevention of child abuse, with the objective of laying the foundations for the discipline of clinical forensic medicine in Japan.

3. Forensic Toxicology

Using LC/MS/MS and LC/QTOF-MS the methods to detect illegal drugs are investigated. We also conduct study on the post-mortem redistribution of some drugs by experiments using animals. We try to figure out the standardized method of drug testing in the field of Japanese forensic medicine.

4. Forensic Odontology

A new method of personal identification (age estimation and DNA testing) and drug analysis using a single tooth at once is developed.

5. Forensic Genetics

We try to find gene alterations that cause a sudden death of an individual. We also try to figure out new methods to predict the birth place of the cadaver by analyzing the DNA types of parasites.

6. Forensic Radiology

Using 3D-CT, we develop new methods to perform stature and sex estimation using the measurements of various bones. We investigate the

merit and demerit of post-mortem imaging to determine the cause of death.

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Department of Biomedical Informatics

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Introduction and Organization

The Department of Medical Informatics and Economics aims to reform medical systems and make social contribution by applying information technology to medical field such as medical economics and hospital management. The department develops basic methods that are applicable to medical information systems in the boundary area of healthcare and information science, establishes infrastructures for information environment where medical information are utilized effectively, and applies knowledge and technique acquired through these efforts to medical and healthcare field.

The main keywords of the target domain are medical and clinical information systems, next-generation electronic health record systems, virtual health care environment, computer representations and standardization of medical concepts, ontology, medical knowledge engineering, hospital epidemiology, quality assessment of healthcare, clinical and bioinformatics engineering, privacy protection and encryption, analysis of hospital management, safety management in healthcare.

The professor of the department also holds the position of director of the department planning, information and management (DPIM) in the University of Tokyo Hospital. DPIM is the department that deals with information analyses and future planning for the

University of Tokyo Hospital by using information systems as well as the planning, design, development, and operation of information systems for the whole hospital. The DPIM was newly established on April 1, 2003, after integration of the Hospital Computer Center and the project team for hospital development, which separately existed until the end of March, 2003.

Since the professor runs the Department of Medical Informatics and Economics with staffs of DPIM, they are practically the same organization. Therefore, educations and researches in the graduate course are promoted together with DPIM activities. The origin of the Department of Medical Informatics and Economics dates back to 1983 when the hospital computer center was officially approved as one of the central clinical service facilities in the hospital. At the same time, the doctor's course for medical informatics was established. The first professor was Dr. Shigekoto Kaihara, who is the founder of medical informatics in Japan. In accordance with the reform to the university with graduate school curriculum in the university of Tokyo, the Department of Medical Informatics and Economics was established in present division of social medicine in 1997. Then, one professor and one associate professor belonging to the hospital computer center moved to the department. In 2000, medical informatics field was set up in the Interfaculty Initiative in Information Studies, Graduate School of

Interdisciplinary Information Studies. The department is located on the fourth floor in Administration and Research Building in the University of Tokyo Hospital.

Teaching activities

- 1). 4-year Ph.D. Course in the Department of Medical Informatics and Economics at the Division of Social Medicine: The Department of Medical Informatics and Economics at the Division of Social Medicine offers the Medical Sciences doctoral course (4-year program) and admission is open to those who graduate from a 6-year program at the Faculty of Medicine (the School of Medicine), and those who complete the master course either in the University of Tokyo or any other institutions (not necessary to be a doctor). Students will acquire Doctoral Degree (Ph.D.) of Medical Science with completion of required units and passing a doctoral thesis.
- 2). 3-year Ph.D. Course and 2-year M.H.S course in the Department of Health Informatics at the Division of Health Sciences and Nursing: The Department of Medical Informatics and Economics is a collaborating department with the Division of Health Sciences and Nursing at the Graduate School of Medicine, and it is called the Department of Health Medical Informatics. At the Department of Health Medical Informatics within the Division of Health Sciences and Nursing, the department offers the Master course in Health Science and Nursing (2-year program) and the Health Sciences and Nursing doctoral course (3-year program). In the master course, students will acquire Master of Health Sciences with completion of required units and passing a master's thesis. In the doctoral course, students will acquire Doctor of Health Sciences (Ph.D.) with completion of required units and passing a doctoral thesis.
- 3). 2-year M.P.H and 1-year M.P.H in the Department of Health Informatics in the School of Public Health: We offer 2-year Master of Public Health (M.P.H) course and the 1-year M.P.H program in the School of Public Health. See the homepage of the School of Public Health.
- 4). 2-year M.M.S in the Department of Health

Medical Informatics in the Medical Science Graduate Program: Graduate School of Medicine, the University of Tokyo, offers the master course in Medical Sciences. The course was established for students who graduate from faculties other than a 6-year program at Faculty of Medicine and eventually wish to advance to the Medical Sciences doctoral course of the University of Tokyo.

The students in FY2019 are eleven in doctor's course for Biomedical Informatics.

The researches cover various topics; development of medical decision support system, analysis of medical human resources in Japan, research for medical and e-Phenotyping in large healthcare database, etc.

Research activities

The research domains are 1) application studies on developments of clinical information systems, hospital information system and electronic health records system, 2) medical knowledge discovery from databases of hospital information system, 3) structured representations and standardization of medical terms and concepts, 4) privacy protection and security in healthcare information systems, 5) mobile health that supports self-management of lifestyle-related diseases.

In these domains, one of the major research topics is joining the University of Tokyo COI (Center of Innovation) Project named "Self Management of Your Health". The COI project aims to construct and deliver an infrastructure for the enhancement of clinical database research and the standardization of nation-wide health information systems. The department plays a role of the development as a sub-project leader. The use of SS-MIX2 standard and extensive storage system is key technology for converting vendor-proprietary database format into the international standard format and facilitating easy multi-purpose secondary use for clinical researches and other researches in social medicine area.

Other various project for standardization of medical or health information systems, creating big database in healthcare domain, developing the national healthcare information database (MID-NET database) for detecting adverse event of drugs, etc.

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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 Ryoza 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, 10 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 2020, a total of 1,653 patients were newly admitted to our hospital ward of 61 beds. The average duration of hospitalization was 11.1 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 2019, 15 patients underwent heart transplant (total 153 cases). In March 2014, our facility was also authorized to perform lung transplantation. Coronary angiography was performed in 1,875 patients, of which 371 patients underwent percutaneous coronary interventions. CT coronary angiography and cardiovascular MRI were performed in 676 and 134 patients, respectively. With regard to arrhythmias, there were 283 cases of catheter ablation, 142 cases of implantation or replacement of pacemakers and other specialized pacemaker devices, including 27 cases of implantation or replacement of implantable cardioverter-defibrillator and 24 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 162.6 patients visit 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, pulmonary hypertension, congenital heart disease, valvular heart disease, arrhythmia, Marfan syndrome, cardiac amyloidosis, and onco-cardiology. 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: analyses of pathogenic mechanisms and development of novel therapies (e.g., gene therapy)
2. Interplay between organs, cells, and molecules in chronic inflammation
3. Mechanisms underlying cardiorenal association
4. Role of hypoxia signaling in cardiovascular diseases
5. Genetic analysis of inherited cardiomyopathy
6. Experiments on pathophysiology of cardiomyopathy using human iPS cells
7. Investigation of disease pathophysiology and development of novel therapies (severe heart failure, cardiac transplantation, congenital heart disease, etc.)
8. New treatments for structural heart disease
9. Diagnosis and treatment of Marfan syndrome and adult congenital heart disease
10. New treatments for pulmonary hypertension
11. New treatments for congenital heart disease
12. Aerobic threshold and cardiac rehabilitation
13. Imaging techniques (echocardiography, MRI, CT, and SPECT) in cardiovascular diseases
14. Epidemiology and prevention of cardiovascular disease
15. Artificial Intelligence in Cardiology

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Department of Respiratory Medicine

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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 professors. At The University of Tokyo, affiliated hospitals and other institutions, approximately 70 members belong to the Department. At the University of Tokyo Hospital, 24 physicians belong to the Department.

Mortality from respiratory diseases such as primary lung cancer and COPD is expected to continue to increase, advancement of respiratory medicine research is necessary. We conduct basic and clinical research for a wide variety of respiratory disorders including primary lung cancer, COPD, asthma and interstitial lung diseases. We have focused on molecular mechanisms underlying the pathogenesis of lung disorders. Our research goal is to develop novel diagnostic and therapeutic modalities for better management of these pulmonary diseases.

Clinical activities

The Department of Respiratory Medicine is responsible for out-patient care as well as care of in-patients (35 patients on average) on the 13th floor of the hospital ward A at the University of Tokyo Hospital. We have two teams consisting of junior residents, two fellows, and an experienced attending.

In-patients are mostly admitted for primary lung cancer. Other diseases include respiratory infections, interstitial pneumonia, and COPD. Many patients with primary lung cancer also have co-existing interstitial pneumonia or COPD. There are many emergency visits and admissions from pneumonia, respiratory failure due to exacerbation of COPD or interstitial pneumonia, progression of lung cancer, etc. In cases of severe respiratory failure such as severe pneumonia and ARDS, we provide ventilatory support in collaboration with the ICU staff.

A specialized clinical conference for respiratory disease has been held once a week since the late 1990s, where staff from our department, Department of Thoracic Surgery, and Department of Radiology join and discuss together to determine the best diagnostic

and therapeutic approach to individual patients. This conference has been highly appreciated as a prototype of Cancer Board of the University of Tokyo Hospital, and, is now held as Respiratory Cancer Board. This conference is still one of the most frequently held Cancer Board at our hospital. Our department contributes to the pre- and post-surgical evaluation of respiratory functions, and also provides consultation on respiratory problems from almost every department at our hospital.

Together with the Department of Infectious Disease, we are responsible for taking care of COVID patients and infection control measures. We supervise the clinical teams that take care of inpatients with moderate COVID-19, make decisions on PCR testing and infection prevention practices, and run the fever clinic for patients who visit our hospital on a regular basis.

At present, primary lung cancer is the leading cause of cancer death, and is one of the major medical and social problem to be overcome. Recently, the remarkable effectiveness of molecular-targeted therapies in primary lung cancer attracted much attention in both basic science and clinical practice. Pneumonia is the 3rd leading cause of all deaths when combined with aspiration pneumonia, and COPD is also a major cause of death. No effective therapeutic modalities are currently available for many respiratory diseases. For example, mortality of acute respiratory distress syndrome (ARDS) is extremely high despite intensive care using currently available tools. Idiopathic pulmonary fibrosis is a progressive and fatal inflammatory and fibrotic disorder of the lung parenchyma, and only a few medications are currently available to treat the disease. Our focus is to develop a novel and potential therapeutic approach to these diseases.

Total numbers of in-patients in 2020

1. Primary lung cancer	398
2. Other cancers	43
3. Abnormal lung shadows	53
4. Interstitial pneumonia	64
5. Respiratory infections	35
6. Non-tuberculous mycobacterial infections	9
7. COPD	11

8. Bronchial Asthma	1
9. Pneumothorax	7

A weekly chart round and professor's round are scheduled every Tuesday afternoon.

A specialized clinical conference for patients with respiratory diseases is held as Respiratory Cancer Board every Thursday evening, together with thoracic surgeons and radiologists. At this conference, radiological diagnosis, indication of CT-guided biopsy and thoracoscopic biopsy, and treatment strategies not only about thoracic malignancies but also other respiratory diseases are discussed, making it possible to give the best care to every patient.

Teaching activities

For medical school education, our department takes part in systematic lectures and specific learning for diagnosis and treatment of respiratory diseases for the 4th year medical students, clinical clerkship for 5th year medical students, and clinical lectures for 5th and 6th year medical students. During elective clerkship for 5th year students, students visit and learn from one of several leading affiliated hospitals in Tokyo.

During systematic lectures, the concept, pathogenesis, pathology, diagnosis, and treatment of common respiratory diseases are comprehensively presented. During clinical lectures, we present clinical cases of important diseases such as primary lung cancer and pneumothorax, and discuss several important points on the diagnostic evaluation and treatment in collaboration with the Faculty of the Department of Thoracic Surgery. Recent major advances in the relevant fields are also reviewed.

During clinical clerkship, each student, as a member of medical care team, has opportunities to experience the daily clinical care with residents and fellows as well as with the faculty. Each student learns how to perform a medical interview, perform physical exams and make plans for diagnosis and treatment. Respiratory specialists provide lecture on chest X-ray as an essential element in clinical clerkship, which is highly popular among the students. Elective clerkship during the 5th year of the educational program is designed to facilitate the exposure to a wide range of

clinical practice both at The University of Tokyo Hospital and at one of the affiliated hospitals for two weeks each (although COVID-19 pandemic made the latter unavailable in 2020). Several lectures on respiratory diseases are also provided.

As for post-graduate education, respiratory physicians (fellows and one attending) assemble a team with residents, and provide medical care for patients with various respiratory diseases. Under these process, residents acquire knowledge and skills required for diagnosis and treatment of respiratory diseases. Seminars on important themes such as medical treatment of lung cancer, diagnostic chest imaging, etc. are held at regular intervals.

Research

Our department conduct basic and clinical research for various respiratory disorders including primary lung cancer, COPD, asthma, interstitial pneumonia, and respiratory infection. Epidemiological, clinical, cellular, and molecular techniques are utilized for the elucidation of pathogenic mechanisms and for the development of novel diagnostic and therapeutic modalities in respiratory medicine. Postgraduate students as well as faculty members study genetic and epigenetic alterations in lung cancer, cell biology using airway epithelial cells, fibroblast and smooth muscle cells, both in collaboration with the Faculty of the Department of Thoracic Surgery. Genetically engineered mice are also used as disease models. These results have been presented and published in scientific meetings and peer-reviewed journals. Our main research projects are as follows.

- Search for diseases-susceptibility genes and elucidation of their pathophysiological roles in respiratory diseases
- Analysis of disease-models using genetically engineered mice
- Analysis of DNA methylation, histone modification and miRNA in lung cancer
- Search for previously unidentified oncogenic driver mutations in lung cancer and elucidation of resistant mechanisms to molecular-targeted drugs
- Analysis of functional alterations of airway epithelial cells and fibroblasts in relation to tissue repair and remodeling, e.g., epithelial-mesenchymal transition, and the roles of various cytokines and chemokines, in asthma and COPD
- Detection of small airway disease using impulse oscillometry and its clinical application
- Search for predictive factors for responses to chemotherapy in malignancy including lung cancer
- Epidemiological study of respiratory diseases, using Diagnosis Procedure Combination database.

Takahide Nagase is a GOLD Assembly member.

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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 associates, 18 fellows, 68 graduates, and other visiting researchers including students from abroad. Some others are under a temporary transfer inside and outside the country. The North and South wings on the 11th floor of Ward A have provided core hospital

rooms for the department. Laboratories of the department are scattered on each floor, mainly of Clinical Research Center.

Clinical Activities

The Department of Gastroenterology is in charge of about 80 inpatients on average, which are about 2,700 in total per year. We receive about 110 new patients each week in and out of the hospital, with an average hospital stay of 10.6 days. Resident, junior and senior staff members bear the responsibility for the medical management of each inpatient in collaboration with subspecialty groups concerned. The staff members examine about 4,600 outpatients with

various digestive diseases in a month. Specialty and subspecialty clinical conferences are held on Monday evening.

Hepatocellular carcinoma is the most common disease in patients who are admitted to the department (~400 cases in 2020). The number of treatments for hepatocellular carcinoma, represented by percutaneous radiofrequency ablation, nearly 250 cases per year, 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 departments is actively performed: 1) ESD for superficial pharyngeal cancer is often performed in cooperation with the department of otorhinolaryngology; 2) ESD for duodenal epithelial tumor with the support of the Department of Gastrointestinal Surgery, 3) as for Non-exposed endoscopic wall-inversion surgery (NEWS), which was developed with the Department of Gastrointestinal Surgery, its clinical indication has been now expanded from the resection of GIST to the treatment of gastric cancer. In 2021, 'Endoscopic full-thickness resection for submucosal tumor' has been approved as a highly challenging novel medical technology with the support of the Department of Gastrointestinal Surgery. Our challenge to novel endoscopic procedures continues. Double-balloon endoscopy (DBE) and capsule endoscopy (CE) enabled the examination of whole small intestines (approximately 100 cases in 2020). Especially in inflammatory bowel disease (IBD) patients, we perform the examination using an optimal method including DBE, CE, and MR enterography. In severe IBD cases, we conduct the combination therapy of conventional immunosuppressive drugs and the latest biologics to increase QOL and achieve mucosal healing and prevention of relapse. About 400 metal stent placements for malignant gastrointestinal obstruction have been performed at our facility. All those interventions are performed by the members of our department, who are specially trained for each technique. In addition, for the management of inoperative malignancies, we effectively combine the interventional treatments with various chemotherapy regimens including immuno-checkpoint inhibitor. Aiming at personalized medicine based on genetic information, we are also actively conducting cancer multi-gene panel testing.

On an outpatient basis, the number of performed 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.

Educational 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, 68 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 gastroenterological disorders. The themes of our recent basic

researches include the study on carcinogenesis in gastroenterological neoplasms, mechanism of viral hepatitis infection, the pathogenesis of metabolic liver diseases, liver regeneration, liver fibrosis, pathogenesis of *Helicobacter pylori* infection, molecular characterization of gastrointestinal morphology, establishing new animal models, tracing cell differentiation, and stem cell biology for various diseases in our area. Using new concepts such as transparent organs, genomic and epigenomic profiling of clinical samples, organoids, or liquid biopsy, we perform various experiments to translate the basic results into clinics eventually.

Various clinical activities are recorded in database and analyzed. Studies oriented toward evidence-based medicine are highly appreciated. Recent studies include 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.

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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 30 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 30 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, epigen-

etics, 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-HCO₃ 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.

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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 25 beds mainly on the 12th floor of the North

Wing Ward A of the University of Tokyo Hospital, and took care of 403 new inpatients per year. 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, Project Assistant Professor: Dr. Jun hosoe [until Oct 2020]), Genomic Research Support Center (Project Associate Professor: Dr. Nobuhiro Shojima), 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 [until Apr 2020]), 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 13 students of Graduate School in our division. With all these 53 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 136 patients per day (total 33,026 patients per year). On the inpatient ward, we not only take care of around 25 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, exercise 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

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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 hemato-poietic 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.
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.

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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

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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 11th 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, *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 undergraduate medical students according to the educational programs of the University of Tokyo. For the fourth year medical students, six lectures of infectious diseases are given. In addition, principles of medical diagnosis are taught at the bedside. During the 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 researches 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, such as *Clostridioides difficile* 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

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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 associates, one research associate, and 5 adjunct professors, and other members are 4 senior residents, 16 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 2020 April to 2021 March, overall 2,603 patients (99 individuals) were admitted to the ward, all of whom were eating disorder patients. Outpatient clinic is attended on every morning and afternoon in three consultation rooms by approximately fifteen

physicians. During 2020 April to 2021 March, the numbers of the new outpatients and of the overall outpatients in our department were 144 and 4,119, 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 psychopathology 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.

Sixteen 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.

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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 transplantation and organ transplantation;
- III. Clinical work

- 1) Pre-operative autologous blood collection and preservation;
- 2) Collection and preservation of peripheral blood stem cells for transplantation;

Teaching activities

Sixth-grade medical students are provided with practical courses focusing on clinical practice of blood transfusion and laboratory tests. Courses are given in small groups of 6 students each, in a total of 18 groups per year. The course lasts 5 days/week, including the following subjects;

- 1) Visit to the laboratories of the department to understand the routine of a laboratory;
- 2) Introduction to the blood group types (red cells, platelets, leukocytes) and their importance in transfusion medicine and in transplantation (bone marrow and organ);
- 3) Methodology of blood typing and compatibility testing for transfusion;
- 4) Methodology for screening of irregular antibodies, and their importance in transfusion practice;
- 5) Introduction to the post-transfusional complications, their etiology, prevention and treatment.
- 6) Introduction to the preventive measures of blood borne viral transmission, especially focusing on the NAT test and the look-back survey.
- 7) Acquisition of informed consents related to blood transfusion, using the role playing method.
- 8) The indications and techniques of autologous blood collection and preservation;
- 9) The techniques for peripheral blood stem cells (PBSCs) collection and preservation, as well as their clinical application;
- 10) The recent advances in the field of blood transfusion, including the “Blood Law”, and the recently revised “Indications of blood products” and “The principles of transfusion practice”.
- 11) One-day visit to the Japanese Red Cross Blood Center, to learn the general process of blood donation and transfusion, including the types of blood products, and their indications.

Research activities

Research on red cells, leukocytes, and platelets, the post-transfusional complications, transplantation im-

munology, 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.

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Reproductive, Developmental and Aging Sciences

1. Obstetrics and Gynecology

Department of Reproductive Endocrinology

Professors

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Associate Professors

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Organization

The Department of Reproductive Endocrinology is organized by Professor Tomoyuki Fujii. 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 200 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.

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Department of Gynecologic Oncology

Associate Professor

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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

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Department of Perinatal Medicine

Associate Professor

Kaori Koga

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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.

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Department of Molecular and Cellular Reproductive Medicine

Professor

Yutaka Osuga

Associate Professor

Osamu Hiraike

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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 annually. We specifically focus on the role of inflammation and transcription machinery in these issues. Senescence and aging process are also extensively investigated.

- 1) The mechanism of folliculogenesis, follicular atresia and intrafollicular microenvironment in the ovary.
- 2) The physiological functions of sex steroid hormones and gonadotropins.
- 3) The molecular mechanisms of endometriosis.
- 4) The molecular mechanisms of uterine fibroid and adenomyosis.
- 5) The effects of aging and cellular senescence on the reproductive system.

In clinical section, we have an out-patient clinic for infertility, gynecological endocrine disorders and genetic counseling. We also perform minimally invasive surgery for benign gynecological diseases

including endometriosis, uterine fibroid, adenomyosis, infertility, and pelvic organ prolapse. More than 90% of surgery cases for benign gynecological disorders are operated using endoscope, and we deal with more than 400 cases annually.

In accordance with the notion of life stage specific approaches, we also manage patients complaining primary/secondary amenorrhea, infertility, dysmenorrhea, heavy menstrual bleeding, and climacterium. Osteoporosis in their 10's to 20's and perimenopausal age could be a heavy burden for patients and we have already established the primary care system for these women. Numerous number of female athletes refer to our clinic as well.

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Reproductive, Developmental and Aging Sciences

2. Pediatric Sciences

Department of Pediatrics, Department of Developmental Pediatrics

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(As of March 31, 2021)

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Introduction and Organization

The former Department of Pediatrics developed into 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 professor, 4 lecturers, 1 project lecturers, 23 associate professors, 3 project research associates, 5 senior residents, and graduate students on March 31, 2020.

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. Offices are on the second and third floors of the East Research Building.

Our laboratories are 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. In addition, patients regarding 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 have specialized clinics covering 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). There are 21 beds in the NICU and 36 beds in the growing care unit (GCU). There are 12 beds in the PICU and our institution is going to fulfill the designation as children's hospital affiliated to the university hospital. In the NICU, we are taking care of small premature babies weighing from 400g to 4,000g often associated with congenital disorders requiring invasive interventions.

PICU is one of tertiary centers of pediatric emergency covering the east part of Tokyo. The PICU provides advanced monitoring and comprehensive care for children facing 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 for any child who needs it. We care for children facing a full range of severe and complex medical conditions, including: Severe infections, such as sepsis and pneumonia, 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.

In general ward of the Pediatric Medical Center, we treat 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 in the wards.

Cardiology; We use the most comprehensive heart tests and treatments to deliver the highest quality care from admission, to discharge, to follow-up, and our services range from fetal cardiology to cardiac disease prevention to pediatric interventional cardiology to heart transplantation.

Neurology; We are part of several multidisciplinary teams, including those that treat: childhood stroke, hypoxic ischemic encephalopathy and other neuro-logical disease.

Hematology/Oncology; A multidisciplinary team of experienced healthcare providers will care for children. Approximately 10 patients received hematopoietic stem cell transplantation every year. There are patients with severe combined immunodeficiency, aplastic anemia-syndrome, relapse/refractory acute lymphoblastic leukemia, acute myeloid leukemia and high-risk neuroblastoma. Genomic medicine is also provided. Our team includes: Pediatric hematologist/oncologists, Stem cell transplant physicians, Nurse specialists, Nurses, Social workers

Kidney disease, Endocrinology; Our team has many years of experience and a great depth of knowledge about kidney diseases affecting children and adolescents. Furthermore, the Division of Endocrinology at The University of Tokyo Hospital treats more children with hormone (endocrine) disorders

At Department of Pediatrics, we pay for all treatment; McDonald House housing for families with

options for bigger accommodations with low price staying. Our onsite 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 long in the hospital. We provide an official in-hospital school "Kodama Gakkyu" where patients receive education and have chances to communicate with other patients as well as their family members. "Niko-niko Volunteer" members, 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 such as a Tanabata festival, a Christmas party and music concerts. All the residents, fellows and nurses participate in these activities. We have two child care specialists in the pediatric ward.

Teaching activities

The second grade students are provided with lectures by the staff members and the visiting lecturers about general pediatrics. The third grade students attend clinical clerkship in the inpatient ward for 2 weeks. During this bedside learning, small-group lessons on various pediatric fields are held every day, some of which are switched to online seminars due to the SARS-CoV2 epidemic. We also offer an elective clinical clerkship course for those who are especially interested in pediatrics in their fourth grade. Observing the outpatient clinic and learning the normal development of children are another goal for the fourth grade students. On the last day of each clerkship, the professor evaluates the students' achievements. We also provide a variety of online contents for students.

Research activities

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

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 reveal novel mechanism of pediatric tumors 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 analyzed pathogenic mechanism of nail-patella syndrome.

Endocrinology and Metabolism group:

We are analyzing genes and mechanisms involved in endocrinology and bone diseases. We analyzed the function of the novel gene identified in a rare congenital disease using model animals and iPS cells. We also analyzed the responsible gene for hereditary rickets and found novel mutations and etiology.

Cardiology group:

To reveal the molecular mechanism of cardiomyopathy, we perform genome-wide association studies and generating animal model for cardiomyopathy. Also we perform hemodynamic analysis for patients with congenital heart disease using clinical imaging modalities.

Neurology Group:

The pathogenetic mechanism of acute encephalopathy is investigated. Using mouse models of tuberous sclerosis, the pathogenetic mechanism of neurodevelopmental disorders is investigated. Based on earlier research, a clinical trial of valganciclovir, an antiviral drug for cytomegalovirus infection has been conducted for infants with congenital cytomegalovirus

infection.

Neonatology group:

Epigenetic changes in cord blood and postnatal peripheral blood of preterm and SGA infants are investigated using epigenome-wide methylation analysis. Influence of microbiome on neonatal immune function is also investigated. Neonatal brain function has been investigated using near infra-red spectroscopy (NIRS) with researchers of Department of Education. Cytokine profiles have been investigated in order to elucidate pathophysiology of several diseases in perinatal period.

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.

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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, three 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 400 patients a year are hospitalized within it. Most operation cases are inguinal hernia, but we manage other cases such as respiratory surgery disease, neonatal digestive organ obstructions, infant malignant tumors such as Wilms' tumor and neuroblastoma, biliary tract diseases such as biliary tract dilatation and biliary atresia, respiratory anomalies such as tracheal stenosis and lung cysts, gastrointestinal anomalies, and urological disorders including hydronephrosis and vesicoureteral reflux.

We work with other pediatric surgery teams at other institutions who perform endoscopic surgery (laparoscopic surgery/thoracoscopic surgery). We have developed an endoscopic surgery technique for pediatric diseases not covered by insurance, for cases requiring advanced medical care. Furthermore, we surgically manage seriously ill, mentally and physically handicapped infants, as well as patients with intractable nervous system diseases, to improve their quality of life, and we cooperate with pediatricians (neonatologists) to treat patients with prenatal diagnoses.

Education

We expose first and second year students to our daily clinical work, as well as to our research work, during the "Free Quarter" and "Research Lab Visit" courses. These students are guided to be concerned with clinical areas, and are in charge of parts of various research projects. The students hold a results announcement party at the end of training. For M2 students, general pediatric surgery and neonatal surgery instruction is provided by the associate

professor and the lecturer.

An education program is also provided for M3 and M4 students for five days.

The bedside education of pediatric surgery consists of participation in clinical conferences, attendance at operations, and small group lectures concerning neonatal surgery; pediatric surgical oncology; pediatric hepatobiliary surgery; and pediatric emergency medicine, which includes the practice of performing cardiac massage and intra-tracheal intubation using mannequins for practice.

Additionally, we take charge of the core surgical curriculum during the "super-rotation" postgraduate training. We offer a program in which each resident can learn basic knowledge about pediatric surgical disease and surgery and hemodynamic and respiratory evaluation, as well as basic surgical techniques and patient management strategies.

Research activities

There are two pillars of the research projects in our group recently. One is the elucidation of the course and the development of new therapy of pediatric surgical disease using proteome analysis. The other is the clinical research using NCD (National Clinical Database). The results of these studies has been already announced in some articles.

We concentrate power on the study for the pathophysiology of biliary atresia and approach it from many aspects including an animal model, disease-specific iPS cells, and the search of the biomarkers.

In addition, We now goes a research of the organ regeneration using in-body tissue architecture and start diaphragm and the trachea and gastrointestinal reproduction from bio-sheet or bio-tube technology.

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Reproductive, Developmental and Aging Sciences

3. Aging Sciences

Department of Geriatric Medicine

Department of Aging Research

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Introduction and Organization

The Department of Geriatric Medicine was established in 1962, as the first geriatric department in Japan.

Since elderly patients tend to have multiple organ disorders, these patients should be taken care of as a whole from multiple points of view. In addition, symptoms, signs and responses to the treatment in the elderly patients could be quite different from the younger counterparts. Specific knowledge on the physiological and metabolic changes with aging is necessary when these elderly 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, two 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 elderly 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 elderly
- 6) Clinical study on metabolic syndrome in the elderly
- 7) Biomarkers of dementia, caregiver's stress and geriatric syndromes
- 8) Research on appropriate healthcare for the elderly 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) Role of nuclear receptors in senescence and carcinogenesis
- 14) Molecular mechanism of vitamin K function and its roles in aging
- 15) Diagnosis and prevention of aspiration pneumonia
- 16) Novel roles of antimicrobial peptide, defensin
- 17) Adrenomedullin and airway hyperresponsiveness
- 18) Klotho protein and vitamin D in lung
- 19) Clinical investigation of sleep-related breathing disorder

Publications (Original Articles)

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Surgical Sciences

1. Surgery

Department of Thoracic Surgery

Professor

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Assistant Professor

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Kitano, Kentaro

Konoeda, Chihiro

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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 1997.

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

Six staffs (Nakajima J, Sato M, Kitano K, Konoeda C, Nagano M, and Yanagiya M), 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 2019, Ministry of Health, Labour and Welfare documented that number of deaths from malignant neoplasms was approximately 380 thousand out of 1.38 million total deaths in Japan. Of them, 75 thousand people were killed by malignant tracheal / pulmonary neoplasms. Surgical therapy for non-small cell lung cancer (NSCLC) is thus the most important issue in our department. By the practice of treatment based on EBM, we perform basic training of thoracic surgery for medical school students, graduate students and clinical residents, as well as doing the professional education for training physicians who wish to become board-certified thoracic surgeons.

We have performed video-assisted thoracoscopy for the diagnosis and treatment of the thoracic disease with less surgical invasiveness since 1992 for safer treatment of older patients with cardiovascular and/or respiratory complications. We currently conduct a standard surgery for clinical stage I non-small cell lung cancer (NSCLC), that is, lobectomy and lymphadenectomy through thoracoscopy: Since 2015, more than 90% of patients with NSCLC has undergone thoracoscopic surgery in our department. Research on less-invasiveness, oncological advantage of the thoracoscopic surgery is thus actively done. Robot-assisted lobectomy/segmentectomy with Da Vinci has applied to lung cancer patients since January 2021.

Pulmonary metastasis represents far advanced malignant neoplasms of extrathoracic organs. Pulmonary resection is an option for the treatment of pulmonary metastasis. We actively perform pulmonary resection through thoracoscopy on patients with pulmonary metastasis who are eligible for surgical therapy through thoracoscopy

Thymic epithelial neoplasms, such as thymoma and thymic carcinoma, show broad spectrum in the degree of malignancy. They also associated with paraneoplastic syndromes, such as the myasthenia gravis and the pure red cell aplasia. Although they are relatively rare diseases, we sought to establish the strategies on diagnosis and treatment of these diseases, which are still yet to be determined, from our clinical experiences of more than 200 cases with the diseases in our department. We are now actively participating a multiinstitutional study on malignant thymic epithelial neoplasms database led by Japanese Association for research on the thymus (JART).

Our hospital has been certified as a lung transplant centers since March 2014. We have started to register patients who are eligible for lung transplantation. We successfully performed the first case in Tokyo of living donor lung transplantation in April 2015: The patients had suffered from the interstitial pneumonia. In July 2015, we also succeeded in performing brain-dead donor bilateral lung transplantation on a patient who had suffered from the pulmonary hypertension. We have performed 78 lung transplants (including 17 living related donor lung transplantations) 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 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 (2020)

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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 Monday, Wednesday and Friday. Patient round is on Tuesday. 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 11 Board-certified 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 2021, 155 cases of heart transplantation including 14 pediatric patients and 382 cases of ventricular assist device (VAD) implantation including 249 implantable continuous-flow VADs were performed in The University Hospital with excellent long-term survival.

Teaching Activities

We have the chair of systematic review of cardiovascular surgery in the spring term at the 2nd grade of medical course. We expose the students to daily clinical works as well as research works during the course of “Free Quarter” and “Research Lab Visit”, which are scheduled in the summer and spring vacations at 1st and

2nd grade. Joint lectures with the Cardiology Department are scheduled 3rd through 4th grades. Each student is assigned one or two cardiovascular surgical cases in the Regular Clinical Clerkship, in which he/she is required to learn preoperative patient evaluation and management, surgical treatment and postoperative care, based on participatory practice. There are also fifteen small key-lectures on cardiovascular surgery. Hands-on practice is provided during the Advanced Clinical Clerkship one-month course in the last months of 3rd grade.

We take charge in core surgical curriculum in the “Super-rotation” postgraduate training. We offer a program in which each resident can learn basic knowledge of cardiovascular disease and surgery, and hemodynamic and respiratory evaluation as well as basic surgical techniques and patient management. Residents who take the course of cardiovascular surgery are required three-year general surgical training for General Surgery Board certification. We have well-developed specialty/subspecialty training programs to allow the residents to pass Cardiovascular Board Examination by 9-10th postgraduate year.

Research Activities

In order to achieve excellent clinical results and to seek for new possibilities of surgical treatments, it is essential for cardiothoracic surgical department of the University to have active research programs in clinical and basic subjects. The Cardiothoracic Department of the University of Tokyo has created highly active research programs in the every field of cardiothoracic surgery, played an internationally leading role and contributed to its development. A research meeting is held once a month on a research project for every member of the department to understand and to make free thorough discussions of the subject.

Basic and/or clinical research activities are focused on 1) establishment of recovery and weaning protocols of left ventricular assist device, 2) basic and clinical research on cryopreserved allograft, 3) application of regenerative medicine to end-stage heart failure, 4) analysis of cardiomyocytes matured and differentiated from iPS cells, 5) mechanism analysis of right heart failure and development of effective pharmacological and mechanical therapy, 6) development of versatile

suture device, 7) clinical research to test the safety and efficacy of artificial pancreas during open heart surgery.

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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, transmediastinal (non-transthoracic) radical esophagectomy with extended lymphadenectomy has been applied, which shows less pulmonary complications, shorter postoperative hospital stay and better QOL after surgery. To develop this surgical procedure, we and other surgeons sharing same will established the Japanese Society for Nontransthoracic Radical Esophagectomy in 2016. New methods of endoscopic/laparoscopic full-thickness resection, non-exposed endoscopic wall-inversion surgery (NEWS) has been developed for submucosal gastric tumor as a collaboration of endoscopy and laparoscopy, and now NEWS is applied for some gastric cancer. Elimination of the pulmonary complications after esophagectomy and the detection of minute metastasis for the establishment of better surgery are also our important targets.

Another main research activities of the department of Gastrointestinal Surgery has been focused on

diagnosis and therapy for gastrointestinal diseases and clinical and basic research for gastrointestinal carcinogenesis from the view point of "Surgery and Inflammation". The department's research activities have focused on a wide spectrum of research topics, ranging from basic research topics to clinical ones. Our research activities have been well organized and ultimately achieved by maintaining a close connection between hospital and laboratory activities. Our medical staffs make every effort to promote the research activities and obtain successful results.

Clinical Activities:

We have outpatient clinics from Monday through Friday. We have specialized divisions for outpatient management of esophageal, gastric diseases. The ward is divided into two subgroups, and each of them has one medical staff for supervision, one assistant supervisor, one chief resident, and one or two junior residents in rotation. They are on duty for daily patient care under the supervision of medical staffs. Ordinary, each subgroup takes care of 15-25 patients.

The weekly official activities of our department are Ward Rounds by the Professor on Monday. We have post- and preoperative case conferences on Wednesday, 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 100 gastric and 60 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.

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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, preoperative navigation for hepatic surgery, and clinical application of artificial intelligence and synthetic blood vessel graft.

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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 Tuesday, Wednesday, Thursday and Friday. 1621 operations were performed in 2020. The numbers of main operations are adrenalectomy 19, nephrectomy 25, partial nephrectomy 59, nephroureterectomy 28, radical cystectomy 21, radical prostatectomy 120, transurethral resection of the bladder tumor (TUR-Bt) 251, transurethral resection of the prostate (TUR-P) 11, and Robot assisted surgery 193 (radical prostatectomy 151, partial nephrectomy 40, radical cystectomy 9, pyeloplasty 2).

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 21,567 patient-days from January 2020 to December 2020.

Teaching activities

Systematic urological lectures are provided for second year medical students. Both clinical lectures and bedside 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.

Bedside 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

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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 ten 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 408 surgically treated inpatients in the year of 2020. On Monday, Wednesday and Friday mornings, pre- and post-surgery conferences are held, and the Director's Round takes place after the conference every Wednesday. Operating days are Monday, Tuesday and Thursday. In addition to the clinical conferences, research conferences are held every Monday morning. Each research unit holds its own conference every week. Over 1200 colonoscopies are performed for a year. The newest technologies are introduced for

diagnosis and treatment of colon and rectal cancer and long-term surveillances for inflammatory bowel disease are performed.

Teaching activities

The Department of Surgical Oncology also offers a fellowship in surgical oncology for well-qualified surgeons who have completed their training in general surgery and wish to further specialize in surgical oncology. The Department of Surgical Oncology has a Surgical Oncology Training Program and provides broad reaching experience in technical aspects of diagnosis, treatment and management for adult patients with both surgical and oncologic problems, development of surgical judgment, and increasing knowledge about routine and complex conditions. In addition, the dedicated staff allows multiple opportunities for academic development both along clinical and basic scientific lines.

In the undergraduate education program, our department plays a role in the systemic lecture and in the clinical introduction lecture for the 2nd year medical students. We offer the clinical lectures and the bedside learning program for 3rd year medical students, in cooperation with other departments of surgery. In the systemic lectures on surgery, various fields were covered such as surgical oncology and immunology, injury, somatic reaction to surgery, infectious diseases, shock, pre- and post-surgical management and nutrition. In the clinical lectures, we presented many diseases such as colon cancer, colonic polyp, colonic polyposis and inflammatory bowel disease. In the postgraduate education program, new residents are trained to become qualified surgeons. In addition to pre- and post-surgery clinical conferences, the residents are expected to attend research conferences and seminars, which are held periodically. They are also asked to present cases at clinical meetings, which are held locally such as the local meeting of the Japanese Society of Gastroenterology.

Research activities

We apply the techniques used in molecular and cellular biology to our research. The following are the major themes under research.

1) Preoperative radiotherapy in lower rectal cancer

- 2) Cancer surveillance in ulcerative colitis
- 3) Carcinogenesis in ulcerative colitis
- 4) Laparoscopically assisted colon surgery
- 5) Local immunity in colorectal cancer
- 6) Genetic analysis of colorectal cancer and adenoma
- 7) Prognostic factor of early colorectal cancer
- 8) Surveillance program following colectomy for colorectal cancer
- 9) Analysis of factors associated with conversion surgery in initially unresectable/metastatic colorectal cancer
- 10) Cancer Immunotherapy targeting to the tumor vessels
- 11) Autophagy in Oncology
- 12) Lipid metabolism in carcinogenesis and tumor progression
- 13) Pathological studies in obstructive colorectal cancer
- 14) Genetic analysis on sensitivity to chemotherapeutic agents
- 15) Hemostasis and fibrinolysis in Oncology
- 16) Intraabdominal chemotherapy for peritoneal metastasis of gastric cancer
- 17) Pharmacokinetics in intraperitoneal chemotherapy
- 18) Clinical trials of chemotherapeutic drugs in metastatic colorectal cancer (single- or multi-institutional)
- 19) Single nucleotide polymorphisms (SNPs) in inflammatory bowel disease
- 20) Anatomy of vessels feeding the colon and rectum
- 21) High Frequency Ultrasonography (HIFU) for solid cancer
- 22) Quantitative analysis of intraperitoneal cancer cells in peritonitis carcinomatosis
- 23) Immunomodulation in chemoradiotherapy for locally advanced rectal cancer
- 24) Robot assisted laparoscopic colorectal surgery
- 25) Postoperative defecation function, urinary function, and sexual function after rectal cancer surgery
- 26) Application of 3D images and 3D printers in colorectal surgery
- 27) Navigation surgery
- 28) AI endoscopic diagnosis
- 29) AI pathological diagnosis
- 30) Microbiome in colorectal cancer

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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 arteriosclerosis.
- 7) Pharmacological analysis of microcirculation in in-vivo model
- 8) Mechanism of arteriogenesis in ischemic limb.
- 9) Development of a new drug delivery system for therapeutic angiogenesis
- 10) Hemodynamic analysis after endovascular aneurysm repair
- 11) Introduction of gene into vascular wall cells by electroporation
- 12) Application of nano technology for in-vivo gene transfer to vascular wall cells
- 13) Basic research for arterialization of artificial organ
- 14) Development of a new method for evaluation of limb ischemia
- 15) Development of a new machine for auto-evaluation of in-vivo endothelial function
- 16) Creating strategy for diagnosis of acute aortic syndrome.
- 17) Analysis of ambulatory system and muscle mechanics in claudicants with peripheral artery disease.
- 18) Modeling of saccular aneurysm with the computational simulation.
- 19) Development of hemostatic agent using Tetra-PEG hydrogel.

- 20) Prediction of dilated morphology of aortic aneurysm by airbag simulation.
- 21) Quantification of hand movements during suture using Leap Motion and its clinical feedback.
- 22) Study of intimal hyperplasia using aorta-inferior vena cava fistula model.

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Department of Breast and Endocrine Surgery

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Homepage

Organization

Our section is staffed by one professor, one associate professor, one lecturer, and five associates. Official activities of our sections are run on the same schedule of the Department of Gastrointestinal Surgery.

Clinical Activities

Endocrine Surgery had not been so familiar with Japanese; however, it has been a long time to be studied this area by top level surgeons in western countries. We have started our activities for this area since 1987 and our department has been established with reconstruction of our hospital structure in 1997. This is a result of the growth of demand nationally and internationally and it is caused by not only treatment for malignant disease but also functional one or giving more attention to quality of life.

Professional skill and wider knowledge of endocrine system are required for this area. Diseases we treat at our department are breast, thyroid, and parathyroid. In additional to treatment for malignant cases of these diseases, we perform surgical proce-

dures as well as systemic treatment. We co-work with the department of endocrine internal medicine and have about 250 surgical procedures annually in total.

In breast surgery, more than a half of the mammary cancer patients undergo the breast-preserving surgery. In addition, sentinel node navigation surgery has been adopted, resulting in better quality of postoperative life. Reconstruction surgery for the breast cancer is likely to provide much better QOL. In this field, we have started collaboration with the Department of Plastic Surgery. Chemotherapy, hormone therapy and molecular-targeting therapy play important roles in treatment of the breast cancer. 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 wide areas related to 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 cancer and thyroid cancer.
- 5) Studies in the area of sentinel node biopsy in breast cancer.
- 6) Studies about 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

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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, one associate professor, four lecturers, two 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

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Organization

The present faculty of the Department of Plastic and Reconstructive Surgery consists of 1 professor, 1 associate professor, 1 lecturer, 2 project lecturers, 5 associates, 5 physicians, and 4 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 20 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. 1088 new patients visited our department, including 808 patients in emergency. 1461 surgeries were performed. Each week, the professor goes the round of inpatients on Friday morning. 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.

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Department of Oral-Maxillofacial Surgery

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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, orthognathic 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 orthognathic 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

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- (Review articles)
1. Ogasawara T, EC Ko, J Yu. Application of Stem Cells in the Oral and Maxillofacial Region. *Stem Cells Int*. 2020 Apr 13; 2020:2421453. doi: 10.1155/2020/2421453.
- (Patents)
1. Ma Q, Suenaga H, Masamune K, Kobayashi E: Automatic surgical planning system, surgical planning method, and program (PCT/JP2020/042491)

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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 cooperation with other departments.

Limb reconstruction operations using external fixators included non-union, leg lengthening and

deformity correction. One of the main interests of this group is the development of a system to analyze the mechanical properties of a skeletal system. During this period of analysis, the mechanical properties of the fracture site in vivo are to be evaluated by monitoring the motion of a dynamic pin clamp during simulated walking.

Research activities

Our research activities cover the full range of the musculoskeletal system medicine, using the in-depth sciences of biology and technology. Especially in the field of molecular biology of bone and cartilage metabolism, we are regarded as being on the leading edge in the world. Basic research is performed under the supervision of the faculty staff members. 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.

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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 2200 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 7860 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

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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 otorhinolaryngological diseases and associated systemic diseases, and has specialized clinics in middle ear and inner ear diseases, hearing impaired infant and children, adult and elderly patients, facial palsy, vertigo and balance disorders, olfactory disorders and paranasal diseases, voice and speech disorders, 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 broncho-esophagological 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, bronchoesophagology and rhinology and is related to case research, clinical statistics and clinical electrophysiology. Basic research is also encouraged to solve essence of clinical problems and to elucidate basic phenomena or anatomical and cellular structures. Our research topics cover:

- 1) Morphology and neurophysiology of the inner ear focusing on sensory neural deafness
- 2) 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.

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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 musculoskeletal disorders
- 2) Prognostic evaluation of patients with metastatic bone tumors
- 3) Rehabilitation and long-term outcome in patients with skeletal dysplasias
- 4) Pathology and treatment for patients with congenital limb deficiencies
- 5) Analysis of rehabilitation outcome using DPC data

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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, 2021, the Department of Anesthesiology consists of Professor Kanji Uchida; Associate Professor Masahiko Sumitani; Lecturers Nobuko Ito, Masahiko Bougaki, Yoshiteru Mori, Mitsuaki Muroya, Gaku Kawamura, Taro Kariya; 24 Associates, 18 anesthesiology residents, and 8 graduate students. The outpatient clinic is located on the 2nd floor of Outpatient Clinic Building and the 3rd floor of Central Clinical Service Building 2, the inpatient units are located on the 6th floor north 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 (Apr 2019 – Mar 2020). In FY2020 (Apr 2020 – Mar 2021), however, the

number of surgeries decreased due to the SARS-CoV-2 infectious disease (COVID-19) pandemic, and the total number of surgeries was 9,954, of which the anesthesiologists managed 7,927 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 1,407 preoperative patients in FY2020. 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 decreased from the previous year to 1,110 (1,559 in FY2019) in FY2020 due to dynamic and timely changes in ICU operation in response to the COVID-19 pandemic and a decrease in the number of surgeries as mentioned above.

We 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 FY2020 was 308 (307 in FY2019). The number of neuraxial labor

analgesia decreased slightly to 365 (386 in FY2019) in FY2020 due to the impact of COVID-19.

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 FY2020 was 6,090 (6,508 in FY2019), of which 215 were first-time patients (298 in FY 2019), a decrease thought to be due to the COVID-19. The number of active beds was 1, and the number of inpatients was 18. There were 107 requests for pain consultation for inpatients in FY2020.

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 FY2020 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 99 junior residents of PGY1 and 2 from the General Education Center as rotators (1-2 months each, averaging over 10 junior residents per month) in FY2020. The training includes anesthesia management, preoperative and intraoperative management, and basic skills and knowledge in emergency and resuscitation settings. For the 18 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 organ damage mediated by ischemia-reperfusion injury of a mouse lower limb;
- 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.

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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. In 2017 fiscal year, we had about 6595 ambulance patients out of total 17607 ER outpatients.

The new ER, four times the size of the previous ER was built in November, 2006. The facility has 5 consultation rooms, 4 specialized consultation rooms for dentistry, ophthalmology, otorhinolaryngology and gynecology, 3 resuscitation bays, and 4 observation beds.

2) Intensive care

Staff members specialized in internal medicine, cardiovascular medicine, orthopedic surgery, surgery, neurosurgery or anesthesiology create “the semi-closed ICU” model. We are responsible for the entire care of the critically ill patients (i.e. patients with respiratory insufficiency such as ARDS, with sepsis, with MOF, with shock), post-operative patients, and tertiary emergency patients, placing an emphasis on evidence-based medical therapy. We had 2,300 ICU/CCU patients in the 2016.

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 and 1 day Hospital MIMMS (Major Incident Medical Management and Support) course are 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.

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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, 7 doctoral course students, 8 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.

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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 (2 credits 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.

From FY2016, the industry, academia, and government-collaborative program “Support Program for Biostatisticians” was launched by Japan Agency for Medical Research and Development for “cultivating talent of excellent biostatisticians, supports the efforts of training them through collaboration between graduate schools that conduct school education, and hospitals that conduct practical training.” (AMED website, July 4, 2017) AMED selected the University of Tokyo as one of the 2 centers for conducting the project (principal investigator: Professor Matsuyama). Our department is also officially participating in the program, 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.

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(Only main publications)

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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. Atsuki 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, four project researchers, eleven lecturers from other organizations, and five visiting researchers contribute to department teaching and research activities.

We have six department graduate students. Three 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)

Graduate Courses

- 1) Biomedical Ethics I
- 2) Biomedical Ethics II

In addition to these courses, the department operates lectures, practical training, and joint seminars for research guidance on a regular basis.

Graduate level courses in Biomedical Ethics focus on the analytical study of ethical theories and on the review of several empirical studies within the field and its related areas.

Research activities

The Department of Biomedical Ethics is interested in the current topics of health care ethics. We are currently conducting studies in the fields of biomedical ethics, research ethics and clinical ethics. Methodology is two-folded—theoretical and empirical. While conducting theoretical research on ethics and philosophy of health care, we also have adopted a descriptive approach.

We have recently established The University of Tokyo Center for Biomedical Ethics and Law (CBEL)—a new interdisciplinary and international education research center aimed to address bioethical issues relevant to Japan and the international community. Our center will form an international network by establishing partnerships with research centers overseas (GABEX: Global Alliance of Biomedical Ethics Centers Project). Through these efforts, we will foster the next generation of bioethics experts in policy-making, research, and clinical medicine who are capable of providing international leadership in the future (<http://www.cbhel.jp/>).

Specific research topics include:

- 1) Study of methods for promoting social consensus on topics related to advanced medical technology
- 2) Study of the function and responsibilities of ethics committees in Japan
- 3) Acceptability of advance directives in Japanese society
- 4) Development of evaluative methods for bio-medical ethics education
- 5) Ethical and psychosocial aspects of living related organ transplantation
- 6) Publication of a medical ethics case book for Japan
- 7) Comparative study of clinical ethics in the Asian region

- 8) Historical analyses for the term “bioethics” in the Japanese context

Sumo Wrestling in Japan. pp.100-112.

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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, II (2 credits each)

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.

Advanced Clinical Nursing I (2 credits)

This course offers a critical reading of previous research theories and discussions of relevant areas.

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, 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, the functions of hospital departments, and hospital ward construction.

Nursing Management in the Early Stages of an Emerging Infectious Disease Pandemic

We conducted an interview survey to identify nursing management and schemes to secure nursing staff in the early stage of the COVID-19 pandemic in infected patient acceptance hospitals, cluster infection outbreak hospital/welfare facilities, and non-medical/welfare facilities for mild cases. This study was supported by a special research grant from the Health Labor Sciences Research Grant.

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Department of Family Nursing

Professor

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Lecturer

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Introduction and Organization

This department was established in 1992. Four faculty members currently serve the department: a professor, a lecturer, and two assistant professors. Enrolled at present are 4 doctoral students, 1 master's students, and 1 administrative staff.

Education

1. Graduate Courses, School of Health Sciences and Nursing (credit hours)
 - Advanced Family Nursing I (2)
 - Advanced Family Nursing II (2)
 - Laboratory and/or Field Work on Family Nursing (16)
 - Practicum in Translational Research Nursing (2)
2. Undergraduate Courses for Students in the School of Integrated Health Sciences (credit hours)
 - Family Health (2)
 - Health Communication (1)
3. Undergraduate Courses for Nursing Students in the School of Integrated Health Sciences (credit hours)
 - Pediatric and Child Health Nursing (4)
 - Clinical Practicum in Pediatric and Child Health Nursing (2)
 - Integrated Clinical Practicum in Nursing (1)

Research

Our department researches 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. Development of a Pediatric Quality of Life (QOL) Inventory for children with chronic illness and their parents;
2. Lifetime support for survivors of childhood cancer and their families: treatment and care in their late effects, special needs education, and working;
3. International collaborative research about posttraumatic growth (PTG);
4. Transitional care for children, adolescent and young adult with childhood-onset chronic diseases;
5. Research about prevention of deterioration of postpartum depression, child abuse and neglect;
6. International collaborative research about family polyvictimization;
7. Caregiving burden and utilization behavior of social services in families of children with medical complexity;
8. Livelihood supports for families of elderly people

with dementia;

9. Support for bereavement from family members.

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. Additionally, the department members are conducting and publishing research that explore the various experiences of children with cancer and their families who were extensively affected by the Tohoku Earthquake of 2011.

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 an evidence of its effectiveness. We collaborate with the evidence-based clinic, with regard to research, practice and graduate education.

In addition to our research activities, we hold bimonthly Family Care Group Supervisions, whereby

deeper understanding of family nursing practices is 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

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Department of Community Health Nursing / Public Health Nursing

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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.

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Health Sciences and Nursing

3. Clinical Nursing

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

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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 in order 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 the elderly

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 the elderly 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 examined what combination of services the elderly persons are using and what its related factors are. We will 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 an 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 elderly people

We conduct a 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 society, need to promote Advanced Care Planning, and has been designed institutional plan. By conducting collaborate research in the three countries, we will 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 will develop the 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's 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

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2. Yamamoto-Mitani N, Saito Y, Futami A, Takaoka M, Igarashi A. Staff nurses' evaluation of care process quality and patient outcomes as quality indicators in long-term care hospitals: A cross-sectional questionnaire survey. *Int J Older People Nurs*. 2020 Dec;15(4):e12334.
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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, 19 graduate students (12 in master's courses, 7 in doctoral courses), a project researcher, and 5 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 cover 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 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

This study examines the maternal body composition, lipid metabolic biomarkers, and nutritional intake to optimize weight management and a healthy lifestyle during pregnancy to prevent low birth weight. This study also investigates the effect of physical activity on the mental and physical health of pregnant women. It aims to provide basic data for appropriate health guidance during pregnancy.

2. Development of a support system for reliable childbirth

1) Midwifery care for positive childbirth experiences

This study evaluates care in-hospital midwife-led system and in-hospital midwifery clinic with the aim of building midwifery care for a positive birth experience.

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 relationship between 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 Japan, Australia, and New Zealand

This study is collaboration between the University of the Sunshine Coast in Australia and the Waikato Institute of Technology in New Zealand to create and evaluate midwifery educational content using virtual reality technology.

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 the pelvic floor muscle training program.

2) Risk factors of mastitis and breast abscess among postpartum women

This study uses a health insurance claims database to investigate the prevalence of mastitis and breast abscess among postpartum women and factors associated with their surgical treatment.

4. Development of a support system for women’s health

1) Support for health of 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. This study also explores factors associated with work engagement among working pregnant women.

2) Preconception care

This study uses health check-up database to investigate the prevalence of anemia among women of reproductive age and factors related to the condition.

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 moisturizing skin care improving skin barrier functions among healthy neonates. In addition, we investigate the relationship between newborns’ skin problems and allergies (i.e., food allergy or atopic dermatitis).

2) Effect of skin care 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.

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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, 9 doctoral course students, 3 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; 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.

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Department of Gerontological Nursing / Wound Care Management

Professor

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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 recently established several departments: Department of Life Support Technology (Molten), 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 trans-disciplinary 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 support staff member, three part-time lecturers for undergraduate courses, and seven part-

time lecturers for graduate courses. The student body consists of nine doctoral course students, seven master's course students, and two undergraduate 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 2020, 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 pharmaceuticals required for nursing practice. The main content themes in the 2020 session included:

- a) Introduction to surgical treatment
- b) Introduction to radiology
- c) Surgical anesthesia
- d) Perioperative management

- e) Clinical conditions
- f) Natural history and treatment of diseases
- g) Nursing pharmaceuticals

The above lectures were provided through cooperation from the departments at The University of Tokyo Hospital.

3) Observation of Human Anatomy (A1 in 3rd yr; 1 credit)

The aim of this series of lectures is to gain a deeper understanding of life and learn about human anatomy through a careful examination of "death" and "disease," as conceptual opposites of "life" and "health." The main themes in the 2020 curriculum included:

- a) Introduction to anatomical pathology
- b) Case studies
- c) Introduction to anatomicopathological research
- d) Approaches to anatomical pathology
- e) Anatomy using ultrasound equipment

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 2020 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) Development of nursing skills for realization of infusion therapy without patience
- 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.

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 2020, the practice was conducted online and consisted mainly of online interviews and activities with senior volunteers, case scenario exercises, and lectures on multidisciplinary cooperation in long-term care nursing homes.

7) Bachelor's theses

The following research themes were submitted in 2020:

- “Development of an AI-based fecal retention assessment method for rectal echo videos taken by home care nurses ” (in Japanese)
- “Development of a simple quantitative application of biofilm for use in pressure ulcer assessment” (in Japanese)

2. Graduate course

1) Gerontological Nursing I (S1; 2 credits)

The main theme of Gerontological Nursing I in 2020 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 2020 were as follows:

- a) Dysphagia
- b) Nutrition management under invasive conditions and nutrition therapy for CKD patients
- c) End-of-Life care for the elderly: creating a prosperous last years
- d) How do we tackle aging and skin health?
- e) Can the human body regenerate?
- f) Considering the role of peri-anesthesia nurses from perioperative nursing research
- g) COVID-19 based on skin symptoms, disease treatment based on COVID-19, and how to travel during a COVID-19 epidemic

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

The main purpose of Wound Care Management I in 2020 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 skin; wound healing
- b) Basics of pressure ulcer, nursing efforts regarding wound care
- c) Prediction and prevention of wounds
- 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 2020 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. The topics were as follows:

5) Master's theses

The following research themes were submitted in 2020:

- "Identification of microRNAs responsive to shear loading in rat skin"
- "Factors associated with the local increase of skin temperature, 'hotspots', of callus in diabetic foot: A cross-sectional study"
- "Changes in the subcutaneous tissue and blood vessel of peripheral intravenous catheter placement sites in hematology and oncology: A secondary analysis using ultrasonographic images"
- "Standardization of a standing-position bladder observation technique and bladder urine volume estimation formula using ultrasonography"

6) Doctoral theses

The following research themes were submitted in 2020:

- "Development of a non-invasive urine volume sensor by electrical impedance measurement"
- "Development of the measurement of taurine concentration by the skin blotting: A non-invasive identifying method for chronic dehydration of vulnerable older people in home care setting"

Research activities

1. Activity policy

Our gerontological nursing research focuses on those suffering from geriatric syndromes, such as pressure injuries, incontinence, malnutrition, pain, dysphagia, osteoporosis and dementia. Our wound care management research focuses on pressure injuries, diabetic foot ulcers, skin tears, ulcers with peripheral vascular diseases, and malignant fungating wounds.

The majority of our clinical research has been conducted at The University of Tokyo Hospital. We regularly participate in pressure ulcer multi-disciplinary team rounds.

In May 2020, 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 had been held onsite until 2019, but in 2020, due to the spread of COVID-19, it was held as a webinar for the first time. Since the first state of emergency was declared from April 7, 2020, and the opportunities for interpersonal interactions were expected to be drastically reduced during the Golden Week holidays in May, the webinar was held from May 2 to 5, also to provide psychological and spiritual support to the students and researchers. While many universities and research institutes are looking for new ways to hold conferences and seminars, we held a webinar pioneeringly, and it was very well received with a total of 1,763 participants.

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), and Nottingham Trent University (UK). 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 2020

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

- Early detection of complications of peripheral intra-vascular catheter by thermography
- Development of an insole-type measurement system for the simultaneous measurement of plantar pressure and shear force during gait
- Development of a fitting device for non-invasive positive pressure ventilation oral-nasal mask using a three-dimensional solution
- Development of apps using communication robots for the elderly
- Development of an absorbent pad for the prevention of incontinence-associated dermatitis
- Introduction of text mining to nursing

3) Clinical studies:

- Novel assessment technologies for pressure injuries
- Cross-sectional study of diabetic foot (e.g., ulcers, calluses, fissures, onychomycosis) and its risk factors
- Cross-sectional study of malignant wounds in breast cancer patients and their risk factors
- Survey and international comparison of lymphoedema
- 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
- Cross-sectional study of the skin of elderly people in a nursing home
- Cross-sectional study of the skin of obese people
- 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 ulcer infections
- Survey of the effectiveness of biofilm removal on wound healing
- Cross-sectional study of catheter failure and its risk factors
- 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:

- Research Encouragement Award from the 8th Annual

Meeting of the Society for Nursing Science and Engineering (October, 2020)

Noyori S, Nagata T, Noguchi H, Nakagami G, Kitamura A, Sanada H. Development of an automatic estimation method for skin-tear severity: A study of machine learning method (in Japanese). Proceedings of the 8th Annual Meeting of the Japanese Society for Nursing Science and Technology. 2020;66.

- Conference Award from the 8th Annual Meeting of the Society for Nursing Science and Engineering (October, 2020)

Koyano Y, Nakagami G, Tamai N, Sugama J, Sanada H. Morphological characteristics of skin tears to estimate the etiology-related external forces that cause skin tears in an elderly population. Journal of Nursing Science and Engineering. 2020;7:68-78.

- The 16th Health Society Award "Pioneer Category" (Co-sponsored by Japan Nursing Association and Johnson & Johnson Japan Corporate Group) (November 2020)

Sanada H

- Conference Award from JANS40 (December, 2020) Takahashi T, Murayama R, Nakagami G, Abe M, Matsumoto M, Sanada H. Development of an AI-based care recommendation system using ultrasound images to prevent peripheral intravenous infusion problems (in Japanese). Proceedings of the 40th Annual Meeting of the Japanese Society of Nursing Science. 2020;61.

- International Lymphoedema Framework Japan 10th Anniversary Award (December 2020)

Sanada H, Nakagami G, Dai M

- JWC WUWHS Gold Award, research on Advances in infection and Biofilm, from Journal of Wound Care (February, 2021)

Nakagami G

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- forces that cause skin tears in an elderly population. *Journal of Nursing Science and Engineering*. 2020;7:68-78.
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International Health

1. International Social Medicine

Department of Global Health Policy

Professor

Masahiro Hashizume, MD, PhD

Assistant Professor

Md. Mizanur Rahman, MSc, PhD

Project Assistant Professor

Shuhei Nomura, MSc, PhD

Ashraful Alam, MSc, PhD

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Introduction and Organization

As of March 2021 the department, headed by Professor Masahiro Hashizume, included the following staff complement; one assistant professors (Md. Mizanur Rahman); one project assistant professors (Shuhei Nomura, Ashraful Alam); five post-doctoral fellows; 10 adjunct lecturers; 15 doctoral students; and seven 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, in order 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 with which needs to be published in a peer-reviewed journal. PhD students without MPH

degree 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 global burden of disease
- Global environmental change and health
- Global health governance
- Population aging and its implications to 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 Monday seminar

Every Tuesday, 13:00-15:00 pm

1) Journal club

Students present a brief summary of research articles from the major medical, social science, economics journals, which are relevant for 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

Research on nutrition and dietary policies using DALY as an indicator for increasing healthy life. Joint Research (Ajinomoto Co., Inc.). PI: Shuhei Nomura

Establishing an effective presence at the World Health Assembly in Japan. Research on Global Health Issues (Ministry of Health, Labour and Welfare). PI: Shuhei Nomura

Exposure to air pollution in Japan and its impact on health and wellbeing (Dyson Technology) PI: Shuhei Nomura

Technology based innovative solutions for improving perinatal care utilization: a network meta-analysis (Oxford Policy Management) PI: Rahman Mizanur

Impact of mobile phone short messaging (SMS) intervention on antenatal and delivery care in Bangladesh: a cluster-randomized controlled trial, Grant-in-Aid for Scientific Research (Young Researcher) (Ministry of Education, Culture, Sports, Science and Technology). PI: Rahman Mizanur

Projections of excess mortality due to climate change - a multi-country environmental epidemiology study. Grant-in-Aid for Scientific Research (B) (Ministry of Education, Culture, Sports, Science and Technology) PI: Masahiro Hashizume

A comprehensive study of the burden of disease in Japan. Grant-in-Aid for Scientific Research(A) (Ministry of Education, Culture, Sports, Science and Technology). PI: Kenji Shibuya

Selected Publications

1. Sera F, Hashizume M, Honda Y, Lavigne E, Schwartz J, Zanobetti A, Tobias A, Iñiguez C, Vicedo-Cabrera AM, Blangiardo M, Armstrong B, Gasparrini A. Air conditioning and heat-related mortality: a multi-country longitudinal study. *Epidemiology*. 2020;31(6):779-787.
2. Zeka A, Tobias A, Leonardi G, Bianchi F, Lauriola P, Crabbe H, Vardoulakis S, Guo Y, Honda Y,

- Gasparrini A, Hashizume M, Vicedo AM, Knudsen LE, Sera F, Ashworth M; Scientific Committee of the International Network of Public Health and Environmental Tracking. Responding to COVID-19 requires strong epidemiological evidence of environmental and societal determining factors. *Lancet Planet Health*. 2020; 4(9):e375-e376.
3. Hashizume M, Kim Y, Ng CFS, Chung Y, Madaniyazi L, Bell ML, Guo YL, Kan H, Honda Y, Yi SM, Kim H, Nishiwaki Y. Health effects of Asian dust: a systematic review and meta-analysis. *Environ Health Perspect*. 2020;128(6):66001.
 4. Nomura S, Kawashima T, Yoneoka D, Tanoue Y, Eguchi A, Gilmour S, Kawamura Y, Harada N, Hashizume M. Trends in suicide in Japan by gender during the COVID-19 pandemic, up to September 2020. *Psychiatry Res*. 2020; 295: 113622.
 5. Nomura S, Kawashima T, Yoneoka D, Tanoue Y, Eguchi A, Gilmour S, Hashizume M. Trends in deaths from road injuries during the COVID-19 pandemic in Japan, January to September 2020. *Inj Epidemiol*. 2021;7(1):66.
 6. Sultana S, Rahman MM, Sigel B, Hashizume M. Associations of lifestyle risk factors with overweight or obesity among adolescents: a multicountry analysis. *Am J Clin Nutr*. 2021 Mar 11;113(3):742-750.
 7. Taniguchi H, Rahman MM, Swe KT, Hussain A, Shibuya K, Hashizume M. Trends and projections of universal health coverage indicators in Iraq, 2000-2030: A national and subnational study. *Soc Sci Med*. 2021 Feb;270:113630.

Department of Community and Global Health

Professor, Academic Leader

Masamine Jimba, MD, PhD, MPH

Lecturer

Akira Shibamura, 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 2021, the members of the department include the department chair and professor, 1 lecturer, 4 assistant professors, 3

secretaries, 12 visiting lecturers, 18 doctoral students, 15 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. Exploring health literacy and its associated factors among Palestinian university students: a cross-sectional study. Sarhan MBA, Fujii Y, Kiriya J, Fujiya R, Giacaman R, Kitamura A, Jimba M. *Health Promot Int*. 2020 Nov 3; daaa089.
2. "Are Filipinos Aging Well?": Determinants of Subjective Well-Being among Senior Citizens of the Community-Based ENGAGE Study. Carandang RR, Shibanuma A, Asis E, Chavez DC, Tuliao MT, Jimba M. *Int J Environ Res Public Health*. 2020 Oct 20;17(20):7636.
3. Effective school-based preventive interventions for alcohol use in Africa: a systematic review. Tomokawa S, Miyake K, Akiyama T, Makino Y, Nishio A, Kobayashi J, Jimba M, Ayi I, Njenga SM, Asakura T. *Afr Health Sci*. 2020 Sep; 20(3): 1397-1406.
4. Seeking connection: a mixed methods study of mental well-being and community volunteerism among international migrants in Japan. Miller R, Ong KIC, Choi S, Shibanuma A, Jimba M. *BMC Public Health*. 2020 Aug 20;20(1):1272.
5. 新型コロナウイルス感染症－ヘルスプロモーションの役割－ 神馬征峰. *日本健康教育学会誌*. 2020;22(2):69-71.
6. Positive Deviance for Dual-Method Promotion among Women in Uganda: A Qualitative Study. Kosugi H, Shibanuma A, Kiriya J, Ong KIC, Mucunguzi S, Muzoora C, Jimba M. *Int J Environ Res Public Health*. 2020 Jul 12; 17(14): E5009.
7. Psychometric properties of an Arabic-language

- health literacy assessment scale for adolescents (HAS-A-AR) in Palestine. Sarhan MBA, Shannon HS, Fujiya R, Jimba M, Giacaman R. *BMJ Open*. 2020 Jun 21;10(6):e034943. doi: 10.1136/bmjopen-2019-034943.
8. The Influence of Breastfeeding Peer Support on Breastfeeding Satisfaction Among Japanese Mothers: A Randomized Controlled Trial. Hongo H, Green J, Shibamura A, Nanishi K, Jimba M. *J Hum Lact*. 2020 May;36(2):337-347.
 9. Depressed mood, suicidal behaviors, and health risk behaviors among youths in the Commonwealth of the Northern Mariana Islands: the 2017 CNMI Youth Risk Behavior Survey. Sakamoto JL, Shibamura A, Jimba M. *BMC Public Health*. 2020 Apr 15;20(1):489.
 10. Factors determining job satisfaction of malaria community microscopists in Palawan, the Philippines: a cross-sectional mixed-methods study. Matsumoto-Takahashi ELA, Tongol-Rivera P, Villacorte EA, Angluben RU, Jimba M, Kano S. *Int Health*. 2020 Apr 14. pii: ihaa015.
 11. Effectiveness of peer counseling, social engagement, and combination interventions in improving depressive symptoms of community-dwelling Filipino senior citizens. Carandang RR, Shibamura A, Kiriya J, Vardelon KR, Asis E, Murayama H, Jimba M. *PLoS One*. 2020 Apr 1; 15(4):e0230770.
 12. Tobacco use and E-cigarette regulation: Perspectives of University Students in the Asia-Pacific. Wipfli H, Bhuiyan MR, Qin X, Gainullina Y, Palaganas E, Jimba M, Saito J, Ernstrom K, Raman R, Withers M. *Addict Behav*. 2020 Mar 28;107:106420.
 13. Positive deviance for dual-method promotion among women in Uganda: study protocol for a cluster randomized controlled trial. Kosugi H, Shibamura A, Kiriya J, Ong KIC, Mucunguzi S, Muzoora C, Jimba M. *Trials*. 2020 March 17; 21:270. doi: 10.1186/s13063-020-4192-8.
 14. Dissemination and implementation of the e-MCH H andbook, UNRWA's newly released maternal and child health mobile application: a cross-sectional study. Nasir S, Goto R, Kitamura A, Alafeef S, Ballout G, Hababeh M, Kiriya J, Seita A, Jimba M. *BMJ Open*. 2020 Mar 9; 10(3): e034885. doi: 10.1136/bmjopen-2019-034885.
 15. Patients help other patients: Qualitative study on a longstanding community cooperative to tackle leprosy in India. Jung SH, Han HW, Koh H, Yu SY, Nawa N, Morita A, Ong KIC, Jimba M, Oh J. *PLoS Negl Trop Dis*. 2020 Jan 13;14(1): e0008016.

International Health

2. International Biomedical Sciences

Department of Human Genetics

Professor

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Assistant professor

Mihoko Shimada, Ph.D.

Project Assistant researcher

James WONG Jing Hao, Ph.D., Saeideh ASHOURI, Ph.D.

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Introduction and Organization

The Department of Human Genetics was established in 1992. Currently, the department has 1 professor, 1 assistant professor, 2 research associate, 2 graduate student, 3 undergraduate students, and 2 research assistants/technicians. 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.

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3. Tanaka, A. et al. Systematic clustering algorithm for chromatin accessibility data and its application to hematopoietic cells. **PLOS Comput. Biol.** 16, e1008422 (2020).

4. Fujimoto, A. et al. Comprehensive analysis of indels in whole-genome microsatellite regions and microsatellite instability across 21 cancer types. **Genome Res.** 30, 334–346 (2020).
5. Campbell, P. J. et al. Pan-cancer analysis of whole genomes. *Nature* 578, 82–93 (2020).

Department of Developmental Medical Sciences

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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 splenic 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.

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Department of Human Ecology

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Introduction and Organization

The Department of Human Ecology was founded when Kenji Uraguchi was appointed to the professorship of the Human Ecology Department on April 1, 1965. Following the retirement of Professor Uraguchi as of March 31, 1966, Professor Haruo Katsunuma (also appointed as 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 as a professor of the Human Ecology program as of April 16, 1979. He founded the theoretical framework of the current human ecology curriculum, which is based on studying the adaptation mechanisms of humans 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 as an associate professor on September 1 of the

same year. Associate professor Ohtsuka established the methodology of 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 as a professor as of April 1 of the same year.

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 as of 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 as of April 1, 2017. Masahiro Umezaki was appointed as a professor as of January 1, 2018. Shoko Konishi was appointed as an associate

professor as of June 1, 2018. Dr. Konishi has been studying the associations between fecundity and fertility and environmental factors from the perspectives of population studies, environmental sciences, anthropology, and sociology.

In fiscal year 2020, the Department had four faculty members: Drs. Umezaki, Konishi, Kosaka, and Takayasu. The Department also had 14 extra-university lecturers delivering lectures in either graduate or undergraduate courses. Professor Umezaki held additional roles in the Network for Education and Research in Asia (ASNET) as well as in the Earth Observation Data Integration and Fusion Research Initiative (EDITORIA) at the University of Tokyo.

Teaching activities

The Department is one of the six Departments of 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. In Human Ecology Special Lecture II, the emphasis is on recent topics and ongoing research in the field of human ecology and related areas. With these classes for graduate students, we attempt to describe human ecology as a basic component of international health, and provide examples of the recent issues that have been dealt with and approaches used in this field. Graduate course lectures are given in English.

The Department is in charge of a part of the School of Integrated Health Sciences, providing undergraduate course lectures on Human Ecology, Environment and Health, Demography, International Health, and Medical Anthropology. We are also responsible for organizing Pharmacology and Toxicology, Physiology, and Environmental Engineering/Human Engineering. At the undergraduate level, our emphasis is on introducing global-scale issues, such as population explosion, food security, and environmental issues, in relation to the problems that the Asia-Pacific region (including Japan) has been facing. Another emphasis is on the relation between human activities and chemical contamination of the environment.

Research activities

Human ecology is the understanding of the human population in the context of their respective ecology as well as in the global context. Most of our research tackles the tasks in the field of Environmental Health and/or Population Ecology [of humans], but with a more comprehensive and broader context. Therefore, we need to adopt different approaches, including fieldwork, experimentation, and GIS (Geographic Information System)/GPS (Global Positioning System) analyses. Our study fields include Asian-Oceanian (including Japan) rural and urban communities, focusing on population, nutrition, growth, environment, and sustainability. Experimental studies on the effects of perinatal exposure to heavy metals have been conducted, emphasizing the factors that modify these effects. Almost all our studies require a transdisciplinary approach. As such, we are collaborating with various local and international research institutes. The following is a list of major activities conducted in the past year.

1. Adaptation to low-protein diet

The inconsistency between Papua New Guinea highlanders' protein-deficient diet 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 in this setting. We have speculated 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 unsolved question of Papua New Guinea highlanders' adaptation to a low-protein diet in a more direct way. In our project, we evaluated the gut microbiota of healthy individuals in four Papua New Guinea communities with different degrees of protein deficiency. The association between gut microbiota and variation in protein intake and nutritional biomarkers was investigated. Shotgun metagenomic analysis further demonstrated that some genes related to nitrogen fixation and urease are enriched in Papua New Guinea communities compared with other countries. Gnotobiotic animal experiments 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 one of the countries experiencing post-demographic transition (i.e., low fertility, aging, and population decrease). Targeting Japanese rural communities, the front-runners of this global issue, we conducted population projection and studies on their food habits, nutritional intake, and subjective perceptions of health. We also conducted a study to identify mitigation and alleviation strategies against 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 the residents' aging, suggested that more older people resided in a house on a steep slope and without direct roadway access.

3. Nutrition and eating behaviors

We have been conducting field surveys every year in the same villages in West Java, Indonesia. Although we did not managed to conduct a field survey in 2020, we performed further analysis and discussion about previously collected data.

4. Interdisciplinary Investigation on the Technology, the Environment, and Fertility

Japan has the highest number of assisted reproductive technology use in the world. Our ongoing project is testing a hypothesis that exposure to technology and environmental chemicals are both linked to increasing infertility in the country. In two hospitals in Tokyo and Tsukuba 198 male participants were recruited. Questionnaire survey was conducted to gather information about lifestyle and sexual function. Urine and semen specimens were collected for quantification of environmental exposure and reproductive biomarkers measurement respectively.

The other part of the IITEF project was the large-scale online questionnaire survey targeting 8,000 men living across Japan. Participants were males aged 20 to 54 years old and responded to questions on socioeconomic status and sexual behavior.

5. Health transition in Lao People's Democratic Republic

Diet in the northern parts of Laos has been characterized by consumption of large amounts of rice with dishes made of wild plants. Wild plants of bitter and even astringent taste, which are supposed to contain more phytochemicals, are preferred over domesticated vegetables. It has been suspected that phytochemicals have roles in nutritional adaptation among the local people through interactions with intestinal bacteria. As the people have gradually been involved in the market economy, their diet has changed toward more consumption of animal meat and oil and less consumption of phytochemicals. We initiated a research project to investigate the potential health impact of such dietary changes in Northern Laos. The questionnaire survey and sampling of biological specimens were conducted in three communities in 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 non-communicable diseases in rural Laos.

6. Potential fetal microbiome transfer from intrauterine exposure

Mounting evidence of bacteria in fertilization products analyzed using DNA-based technologies is challenging the sterile womb hypothesis. We conducted cultivation-based and 16S rRNA sequence analyses using a mouse model in mid and late gestation that suggested the presence of bacteria in fetal, placental, and uterine tissues. This low-abundance fetal microbiome appears to be volatile and transient in nature, in contrast to the relatively stable bacterial composition that matures during infancy. The similarity between the bacterial compositions of maternal and fetal tissues suggests a vertical transmission that 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 the mother and development of immunity in the fetus.

7. Child undernutrition in Cebu, Philippines

Focusing on school children in vulnerable communities, we investigated factors associated with

the nutritional status of children in a rural municipality in Cebu, Philippines. Children aged 6–12 years and their parents were asked to participate. The results showed a high prevalence of stunting and underweight in this community. Children's nutritional status was associated with household income and size, parents' nutritional status, and severe food insecurity. This work has been published.

8. Mouse gut microbiome transitions

Gut microbiome and aging have been discussed based on the average flora of people of different ages. Meanwhile, 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 gut microbiome related to pregnancy and lifespan.

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Department of Biomedical Chemistry

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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, metabo-

lism, 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

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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.

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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.

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Department of Health Communication

Professor

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Associate Professor

Tsuyoshi Okuhara, Ph.D., MPH

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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.

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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

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Associate Professor in health education and health sociology

Naoki Kondo, M.D., Ph.D. (moved to Kyoto University in September 2021)

Lecturer

Daisuke Takagi, Ph. D.

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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 highlights the significance of social determinants of health (SDH) as a key exposure causing social gradient of health. A series of omnibus lectures, each focusing a specific topic of SDH (e.g. income distribution, gender, job stress, and discrimination), are provided by invited lecturers specialized in the field. The course is followed by course II which offers application of concepts into practice through in-class discussion and group works.
- 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 illness, and culture and health.
- 4) Comparative health systems in Asia: Started in 2020, jointly offered by Prof. Soonman Kwon in Seoul National University. The course provides basic frame/theory for comparative analysis of health systems and offers specific country cases for in-class discussion.

2. Undergraduate Courses, School of Integrated Health Sciences

- 1) Introduction to social survey and practice; Provides introductory lecture on sampling, psychometrics, design of social survey and questionnaires. Students are asked to conduct a mini social survey within class on the theme they choose as relevant in their class experience.
- 2) Health and Society (former Health sociology); Lecture series on social model of health generation, social relationship and health, 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).

The department contributed to extend educational environment in the new frame of School curriculum policy, and management of educational duties with limited resources became a challenge.

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 also joined with Departments of Public Health, Medical Informatics, and Health Economics and Clinical Epidemiology the management of National claim Data Base and onsite research center under the contract with the Ministry of Health, Welfare, and Labour to extend empirical healthcare research using a representative big administrative data until 2019. Since 2020, the project is under management by the Department of Clinical Epidemiology and Health Economics, led by Prof. H. Yasunaga.

Dr. Kondo also is an active and leading core researcher in another 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. The team has been developing community diagnosis tool using JAGES data to support participating municipalities to effectively find leverage population for policy intervention. The developed tools have been disseminated and standardized for wider use in municipalities.

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.

Other Social activities

Some faculty members and graduate students contributed to support public health centers and tracing activities by a special section in the Ministry of Health, Labour, Welfare for contact tracing, epidemiology survey, consultation, and patient trajectory. The part of activity results was published in Japanese for reference to support academic-public sector collaboration for risk management under the emergency situations.

Publications

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School of Public Health

3. Health Services Sciences

Department of Clinical Information Engineering

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Introduction and Organization

Information engineering in Japan places a great deal of weight on computer hardware, software, and data processing. It is a discipline that seeks objective data and emphasizes the conception of new methods of data transfer, 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 be used as a tool to help human thinking, such as in presentations, design, and discovery. When computers became connected to each other through the internet, the distribution of information became very easy and rapid, not only within organizations, but also 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 the Ministry of Education, Culture, Sports, Science, and Technology, of Japan.

Teaching activities

The purpose of the Department of Clinical Information Engineering is to nurture talented people who have special knowledge and skills at an international level in order 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 the progress on their own research projects and discuss their future directions.

Research activities

Our research covers the 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 the management and processing of data, information, and knowledge to support the practice and delivery of clinical care. Our laboratory is engaged in the following research activities:

- (1) Computer Graphics & Virtual Reality (VR) for Medical Science: Our research has three goals: (1) to improve the living conditions of in-patients with limited physical activity by providing virtual experiences; (2) to develop new diagnostic methods using medical imaging; and (3) 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.
- (2) Social Information Engineering for Public Health (Public Health Informatics): Our laboratory researches new tools and methodologies for applying information and computer science and technology to public health practice, research, and learning. At present, we are studying differences in the computerization of public health in the US and Japan.

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Department of Global Environmental Health

Associate Professor

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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 since April 2018, and affiliated with the School of International Health (SIH), Graduate School of Medicine since July 2018 as an Associate Department. 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 a short-term effect of environmental risk factors on human health.

This year, we contributed to the postgraduate course under Graduate School of Medicine, entitled “General

Lecture in Medical Sciences X X X II (Basic Tools for Population/Public Health Research) ,” by providing a lecture series on Medical Statistics (Part1).

GEH 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 Tuesday, 11:00-12:30

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

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 including daily time-series database across 19 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. Establishment of an early warning system for malaria incidence in southern Africa
- Asian dust: a systematic review and meta-analysis. *Environmental Health Perspectives* 2020;128(6): 066001.
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Publications

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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 2020, 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 practical training for the Nara Institute of Science and Technology doctoral students and Kobe University School of Medicine 6th-year students (M4); 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.

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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 also have a plan to start a study that applies computational finance to forecast the market value of research and development projects.

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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 osteoarthritis 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

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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. Osteoimmunology is an interdisciplinary research field that investigates the shared mechanisms and crosstalks between the bone and the immune systems. Studies on bone destruction associated rheumatoid arthritis (RA) have highlighted regulation of bone by the immune cells and promoted this field. As seen in the clinical benefits of anti-TNF antibody, anti-IL-6 antibody and CTLA4-Ig on inflammation and osteoclast differentiation for the treatment of RA, the osteoimmunological insight is now of growing importance in clinical applications. It is necessary to comprehensively understand the interplay between bone and immune systems for elucidation of the molecular mechanisms underlying the pathogenesis of various bone diseases (osteoporosis, osteoarthritis, periodontal disease etc.) and immune diseases (autoimmune diseases, infectious diseases etc.).

Osteoimmunology is now emphasized by not only the academic but also clinical sides, and the international competition has intensified in both basic and pharmaceutical researches. This department was founded as a new department focusing on the 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 pathogenesis of various skeletal and immune diseases, and to provide the molecular basis for novel drug discovery in the field.

Teaching activities

As for under-graduate education, our department takes a part in systemic lectures. We train post-doctoral fellows, graduate and post-graduate students in Department of Immunology, Graduate School of Medicine and Faculty of Medicine, The University of Tokyo.

Research activities

By extending the concept of osteoimmunology to various skeletal and immune diseases, we aim to comprehensively elucidate the crosstalks between the bone and immune systems involved in the pathogenesis of the diseases, and provide the molecular basis for novel therapeutic strategies. Our achievement would help to improve the welfare and raise the level of medical treatment in the world.

Main research achievements

RANKL in bone, immunity and cancer

Bone is a dynamic organ that continuously undergoes a process involving resorption and formation (bone remodeling), which are mediated by osteoclasts and osteoblasts, respectively. An

imbalance of bone resorption and formation is often central to metabolic bone diseases, including bone destruction in RA, postmenopausal osteoporosis, bone tumors and osteopetrosis. Osteoclasts are large, multinucleated cells formed by the fusion of precursor cells of monocyte/macrophage lineage. Mature osteoclasts degrade bone matrix proteins by secreting proteolytic enzymes and decalcify the inorganic components of bone by releasing hydrochloric acid. RANKL is an essential cytokine for osteoclast differentiation. RANKL, which are produced by the supporting mesenchymal cells including osteoblasts, osteocytes and synovial fibroblasts, binds to its receptor RANK expressed on osteoclast precursor cells. Mice with a disruption of either *Rank* or *Rankl* exhibit severe osteopetrosis accompanied by a tooth eruption defect resulting from a complete lack of osteoclasts. Mutations in the *RANK* and *RANKL* genes have been identified in human patients with bone disorders such as autosomal recessive osteopetrosis. These genetic findings clearly demonstrate that RANK/RANKL signaling is essential for osteoclastogenesis *in vivo*. We aim to elucidate the molecular mechanism underlying RANKL-induced osteoclast differentiation, in order to develop the novel therapeutic strategies for the treatment of various bone diseases such as RA and osteoporosis (Tsukasaki et al, *J Bone Miner Res*, 2016; Okamoto et al, *Physiol Rev*, 2017). Recently, we have elucidated the mechanism of osteoclastogenesis at the single cell level by single-cell RNA sequencing analysis. Osteoclast differentiation pathway can be divided into multi stages, and we identified a number of genes that determine each differentiation stage. We found that the transcriptional regulator *Cited2* regulates the terminal differentiation step by promoting cell cycle arrest. The single-cell analysis data covering all pathways of osteoclast differentiation would be a useful resource for the development of therapeutic treatments targeting osteoclasts (Tsukasaki et al, *Nat Metab*, 2020).

RANKL plays crucial roles in not only osteoclast differentiation but also the immune system, including lymph node development, thymic epithelial cell differentiation and M cell differentiation in gut. Thus, RANKL is one of the most important factors explicitly linking the skeletal and immune systems.

RANKL is synthesized as a membrane-bound molecule, which is cleaved into the soluble form by proteases. Both forms function as agonistic ligands for RANK. However, the functional difference between the membrane-bound and soluble forms of RANKL had been poorly understood *in vivo*. Thus, we tried to elucidate the physiological and pathological significances of soluble RANKL by generating mice that selectively lack soluble RANKL. Soluble RANKL-deficient mice did not show any discernible osteopetrotic phenotype. In addition, soluble RANKL made no contribution to ovariectomy-induced osteoporosis. Thus, membrane-bound RANKL mainly functions in osteoclast differentiation *in vivo*. Furthermore, unlike RANKL-null mice, soluble RANKL-deficient mice had normal development of the immune organs, including lymph node development, thymic medullary epithelial cell differentiation and M cell differentiation. Collectively, we demonstrated that soluble RANKL is dispensable for physiological regulation of bone and immune systems (Asano et al, *Nat Metab*, 2019).

RANKL also deeply contributes to the pathogenesis of bone metastasis. In bone, tumor cells induce the RANKL expression in osteoblasts through the production of PTHrP and IL-6. RANKL promotes osteoclastic bone resorption, which provides space for tumor expansion and releases certain growth factors from the degraded bone matrices to stimulate tumor growth, forming a vicious cycle. In addition, RANK is expressed at high levels on many different epithelial tumor cells that preferentially metastasize to bone. RANKL acts directly on RANK-expressing tumor cells to increase tumor migration to bone. Notably, soluble RANKL contributes to bone metastasis by exerting a chemotactic activity in tumor cells expressing RANK (Asano et al, *Nat Metab*, 2019). 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. 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-producing T cells (called exFoxp3Th17 cells). exFoxp3Th17 cells display a greater capacity for inducing both synovitis and osteoclastic bone resorption (Komatsu et al, *Nat Med*, 2014). The conversion of Foxp3⁺ T cells into effector T cells has also been observed in various diseases such as diabetes and multiple sclerosis. We have recently demonstrated that exFoxp3Th17 cells also act as osteoclastogenic T cells in alveolar bone destruction in periodontitis. exFoxp3Th17 cells accumulate in periodontitis tissues in response to oral bacteria, and stimulate mesenchymal cells including osteoblastic cells and periodontal ligament cells to

induce RANKL. We found that exFoxp3Th17 cells protect against bacteria by evoking mucosal immune responses as well as removing the tooth (Tsukasaki et al, *Nat Commun*, 2018). Our findings introduce a new concept that bone destruction contributes to the host defense against oral bacteria in periodontitis.

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

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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 three project associate professors, five project research associates and two project researchers, along with a medical staff of approximately 50 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.

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Department of Home Care Medicine

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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., AKTIO Corporation 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 got the third prize for the best clinical department in clinical clerkship program, Faculty of Medicine rated by medical students in 2018.

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 database of patients who receive 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

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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 device (LVAD) is a critical issue which remains to be elucidated. Pulmonary hypertension (PH) is also an important cause of RHF. Now a lot of patients with severe PH are referred to our hospital because the University of Tokyo Hospital has been approved as a lung transplantation center since

2014. We pursue optimal treatment strategy for not only LHF but also RHF.

Clinical Activities

1. Heart Transplant (HTx)

Patients who performed heart transplant in our hospital or in abroad transferred from our hospital are followed up once a month in the out-patient clinic, and undergo repeated myocardial biopsy regularly. When some symptom or findings which suggest rejection are detected, patients will undergo to intensify immunosuppressive regimen in-hospital treatment.

2. Ventricular Assist Device (VAD) Therapy

We recently implant not only extracorporeal pulsatile but also implantable ventricular assist device (VAD). All candidates fell into end-stage heart failure before VAD implantation, and a significant number of them were rescued with heart transplantation or bridge to recovery. We implant centrifugal VAD (EVAHEART, HVAD and HeartMate3) or axial VAD (HeartMate II

and Jarvik 2000) considering patients' physics and clinical status).

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.

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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).

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.

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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., and Fukuda Denshi Tokyo Central Sales 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.

In Japan, cardiovascular death is the leading cause of death in the elderly and is the leading cause of shortening a healthy lifespan. Despite the emergence of various new drugs, new devices, and new treatments, we have not succeeded in reducing cardiovascular death for the last 20 years. We have found that it is important not to study cardiomyocytes alone, but to examine non-cardiomyocytes to consider heart disease (Nature 2007, Circulation Research 2005, Nature Medicine 2017). We also hypothesized that cooperation between the brain and heart maintains cardiac homeostasis, and that failure leads to the onset

of cardiovascular disease and cardiovascular death (Nature Medicine 2017). The idea that the brain regulates the heart is understandable in common sense. Since ancient times, it has been considered, but analysis using current molecular biological techniques has hardly been conducted. We find that the brain controls the heart, and the heart controls the brain and changes each other, mainly through animal experiments. Such a molecular biological approach to brain-heart linkage will understand new cardiac control mechanisms and novel therapeutic targets. Besides, as a therapeutic development, we are promoting research that will develop new clinical approaches such as drug intervention approaches to non-cardiomyocytes, brain imaging diagnosis, and brain stimulation therapy.

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.

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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 lipotrophic 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 lipotrophic diabetes, to facilitate the development of innovative diagnostic, preventive and therapeutic modalities for these diseases, based on resulting research findings and insights.

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Department of Advanced Clinical Science and Therapeutics

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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.

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Department of Medical and Pharmaceutical Community Healthcare

Project Professor

Hirohisa Imai, M.D., Ph.D.

History and Organization Overview

Appropriate drug treatment has not yet been implemented in clinical practice. There are many problems such as polypharmacy, inappropriate drug selection by doctors, and prescribing habits. Therefore, effective institutional design and policy planning for these serious problems have become urgent issues.

In recent years, regional formularies have been implemented in several districts, and the promotion of "standard drug treatment" has begun to take off in Japan as well. The "Japanese Society of Formulary" was established in June 2021 with our department of medical and pharmaceutical community healthcare as the inauguration body.

In health care today, there needs to be more cooperation among doctors and other medical professionals in order to provide patients with an optimal level of care. In particular, if doctors and pharmacists are able to reach a common understanding of a patient's illness, this will allow them to administer an appropriate drug treatment regimen, to perform continuous patient follow-up, and to evaluate the administered treatment accurately. The delivery of optimal drug therapy involves multiple interconnected processes, from investigating what drugs should be used to planning the treatment regimen, assessing treatment compliance and effectiveness, and managing adverse reactions, and only a multidisciplinary, team-oriented approach to health care will make it possible to provide patients with efficient, effective drug therapy. Unfortunately, there are currently few examples of such

"multidisciplinary approaches to delivering optimal drug therapy." Japan is a "super-aging" society and the rapidly increasing number of elderly patients who are taking multiple medications has become an issue of significant concern. Because optimal drug therapy delivery cannot be accomplished through the traditional health care system or through regional health care systems, the construction of a new health care system for the delivery of drug therapy is required.

The interfaces between the systems used in the fields of medicine and pharmacology, and the working relationships between doctors and pharmacists, have gaps; these systems function independently of each other, rendering the design of the overall system inefficient.

For example, although dispensing limits for patients with long-term prescriptions have been discussed in cancer therapy and primary care settings, no theoretical or empirical research has been conducted to study this issue. Nor have any systems been put in place to manage drug therapies based on predetermined protocols for patients with chronic diseases who are in stable condition. In addition, not enough empirical research has been conducted on the development of optimal treatment methods (e.g., optimal patient selection, efficient treatment procedures) based on postmarketing surveillance of expensive drug products.

Against the aforementioned background, the objective of this program is to conduct theoretical and empirical research on the development of new regional health

care and collaborative systems for doctors (hospitals/clinics) and pharmacists (both hospital and non-hospital pharmacists) in order to try to construct a new collaborative system for doctors and pharmacists to optimize the drug therapies that are provided to patients.

In this program, we will plan theoretical research to formulate measures that will support the construction of efficient and effective regional medical care and empirical research using large-scale data, and we will use statistical and epidemiological procedures to analyze medical record data and prescription drug (including medical history) data as well as data from our own epidemiological research in order to investigate systems for delivering effective drug therapy through a multidisciplinary approach, starting with the attending physician and the pharmacist, and focusing specifically on dispensing limits for patients with long-term prescriptions, the introduction of regional formularies, and the introduction of multidisciplinary interventions in the treatment of cancer and cognitive disorders.

This program consists of 1 program professor and 1 assistant program professor. The former is Hirohisa Imai, a specialist in public health and epidemiology who also teaches these subjects, and the latter is Takuya Hirai, Ph.D., a graduate of the University of Tokyo's Graduate School of Public Health and a specialist in collagen disease. Currently, he has returned to clinical practice and is retired. The program also has 2 full-time administrative staff. In addition, graduate students in the professional degree course of the School of Public Health have been involved in this program's research activities and providing teaching support.

Education

The objective of this program is to develop health care specialists who can implement medical collaborations that are suited to a super-aging society. The era when a single doctor is capable of handling all of the care for a single patient is over. The coming age will see physicians, pharmacists, nurses, public health and welfare workers, etc. use a multidisciplinary approach, and collaborate with the government as well, to implement regional, comprehensive health care

systems. This program will train the health care specialists that will be needed for this coming age. In addition, in order to help train the next generation of researchers, this program will be responsible for teaching courses and seminars at the School of Medicine. The Epidemiology courses and seminars will focus on pharmacoepidemiological and pharmaco-economic issues, and provide instruction on how to apply epidemiological approaches to identify problems and formulate responses in regional health care. We will attempt to convey the significance and fundamentals of epidemiology to students with no field experience by exposing them to common scenarios in regional health care.

In the School of Public Health (professional degree course), this program will offer courses in connection with the School of Medicine in, for example, Pharmaceutical Epidemiology, Drug Product Delivery Systems, Adverse Reactions, and the Behavior of Pharmaceutical Companies. As part of their MPH degree research, this program has taught graduate students in the School of Public Health, and performed interventional research on polypharmacy patients until now. Graduate students in the latter stages of obtaining their doctorate degrees, who will be expected to perform their own, independent research in the future, will receive instruction in creating themes for research papers, analyzing data, the handling of literature references, and other basic and critical skills, and will also receive guidance when writing their dissertations on how to develop a consistently logical argument throughout their dissertation as well as on how to properly cite literature references.

Research

This program will utilize primarily prescription drug data (including prescribing histories) and medical record data to conduct theoretical and empirical research focusing on the biostatistical and epidemiological methodologies involved in "the development of new methods of multidisciplinary collaboration for optimizing physician-directed drug therapies."

1. Research on prescription drug dispensing limits for patients with long-term prescriptions

- 1) “Dispensing limits for patients with long-term prescriptions” refers to the practice of having patients who have, for example, received a 90-day prescription go to the pharmacy every 30 days to receive 30 days’ worth of medicine. The pharmacist submits a tracking report to the prescribing doctor when the patient picks up his medicine. This has many benefits in the case of patients with chronic conditions, including making it possible to manage the patient’s drug therapy appropriately, reducing the physician’s workload, managing the quantity of drug remaining, controlling health care costs more appropriately. This program will conduct theoretical and empirical research aimed at establishing a model system that doctors and pharmacists can use in both primary care and oncology to implement dispensing limits for patients with long-term prescriptions.
 - 2) A pilot study on dispensing limits for patients with long-term prescriptions is currently underway (in hypertension, diabetes, dyslipidemia, osteoporosis, breast cancer hormone therapy, and rheumatism). In the future, this program plans to conduct a larger-scale research study with the help of the Ministry of Health, Labour and Welfare.
2. Research on multidisciplinary interventions in drug therapy in regional health care
 - 1) This program will cooperate with regional metropolitan doctors’ and pharmacists’ associations, national health insurance regional branch offices, Japan Health Association branch offices, prefectural health and welfare agency pharmaceutical affairs bureaus, and the like to conduct research on optimal drug therapy interventions for elderly patients. The patients who should receive interventions will be identified by a patient selection board comprised of doctors and pharmacists, and said interventions will be implemented.
 - 2) This program will use prescribing data from health insurance societies to conduct research on implementing notification interventions for optimizing drug therapy in the elderly. The program is conducting research on interventions that attempt to improve drug therapies by sending prescribing physicians and compounding pharmacists written notices informing them of inappropriate prescriptions. The results of such notification interventions will be evaluated after half a year.
 3. Research on the development of methodologies for implementing regional formularies
 - 1) The cost effectiveness of the use of drug products has been called into serious question in recent years, and the efficient use of drug products is being required within the framework of regional comprehensive health care systems. Although formularies may be one effective method of accomplishing this, “Hospital Formularies” and “Regional Formularies” are very different, although they may appear alike, because the latter have many stakeholders, and the implementation of such formularies is therefore extremely difficult. Although regional formularies have not yet been implemented in Japan, this program is conducting research into how they can be developed. This program will investigate, in a quantitative scientific manner, incentives and inducements for promoting data collection and analysis and the screening and use of listed drug products.
 - 2) This program has started to conduct research to assess the effects of introducing regional formularies using certain government-approved “Regional Health Care Collaboration Promotion Foundations.” This program will collect data provided by prefectural health insurance and Japan Health Association offices on patient characteristics, disease names, medical institutions, drugs, etc. and perform an impact assessment on the introduction of regional formularies.
 4. The development of systems for optimizing drug therapies that utilize artificial intelligence

Adverse reactions have many causes, including interactions between different drugs and interactions with the metabolites of certain drugs, and the identification and prevention of adverse reactions requires tremendous effort. Because a

tremendous amount of work is required to investigate the causes of adverse reactions and prevent them from occurring, systems are being developed that utilize artificial intelligence to identify safer and more effective drug therapies. A research team is in the process of collecting and managing a vast amount of data, and working to develop innovative interfaces that will allow doctors and pharmacists to easily make use of artificial intelligence.

Publication

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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 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.

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, cryo

electron 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 spatial and temporal resolution and on these bases try to elucidate functions of molecular motors in vivo combining molecular genetics.

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Department of Molecular Neurology

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Introduction and Organization

Department of Molecular Neurology was established on April 1, 2017 to elucidate the molecular mechanisms based on detailed clinical information and research that integrates comprehensive genome analysis, furthermore, to develop new therapies that can intervene in pathophysiological mechanisms of the neurological diseases and to conduct new clinical trials for the neurological diseases.

Clinical activities

We have outpatient clinic specialized in multiple system atrophy (MSA) cooperating with Department of Neurology. We have started a registry for MSA to establish the natural history of MSA, and, furthermore, to recruit patients to the clinical trial which we are preparing. We also take care of patients in the inpatient's ward cooperating with Department of Neurology. We provide clinical sequencing for patients with neurological diseases to help clinical diagnosis of these patients. We also provide clinical sequencing on referral basis from other hospitals.

Teaching activities

In under-graduate education, we offer opportunities of research experience on molecular genetics

of neurological disorders during the period of the “free-quarter program”. In the post-graduate education, we offer programs for graduate students including molecular genetics, neurobiology and translational researches.

Research activities

Multiple system atrophy (MSA) is a progressive neurodegenerative disease which is characterized by various combinations of cerebellar ataxia and parkinsonism in addition to autonomic failure. No effective therapeutic measures are available. We have been conducting extensive researches on MSA including comprehensive genome analysis on familial as well as sporadic MSA. We have found that a homozygous mutation and compound heterozygous mutations of *COQ2* gene are associated with an increased risk of MSA in multiplex families, and heterozygous mutations of *COQ2* gene are associated with an increased risk of MSA in patients with sporadic disease (Mitsui J, et al. *N Engl J Med.* 2013; 369:233-44). Based on these findings, we considered that supplementation of coenzyme Q₁₀ to patients with MSA could benefit patients because *COQ2* encodes the enzyme essential for the biosynthesis of coenzyme Q₁₀. Recent studies have reported decreased coenzyme Q₁₀ levels in blood, cerebral spinal fluid, and the cerebellum even in MSA patients without *COQ2*

mutations. Based on these studies, we started a multicenter-based (13 institutions) phase II clinical trial (UMIN000031771) to evaluate the clinical efficacy of a high-dose ubiquinol (reduced form of coenzyme Q₁₀) supplementation for suppressing progression of symptoms of patients with MSA in 2013.

To facilitate recruitment of MSA patients into the clinical trial, as well as to establish a detailed natural history of MSA, we started a registry for MSA. To standardize the rating of patients based on Unified Multiple System Atrophy Rating Scale (UMSARS) among the 13 institutions in the phase II clinical trial, we translated the original UMSARS into Japanese with generous help by Dr. Gregor Wenning, the original author of UMSARS. We have also established a method for more sensitive evaluation of the enzymatic activity of *COQ2* mutations (Yasuda T, et al. *Neurogenetics*. 2019 Mar;20(1):51-5).

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Introduction and Organization

Since immune checkpoint blockade therapies were approved for the treatment of many cancer types, remarkable clinical responses have been achieved in a certain proportion of patients. Nonetheless, many patients are unresponsive, and there remain several tumor types that are refractory to immunotherapy. Multiple immunosuppressive mechanisms operate in the tumor microenvironment (TME), and any anti-tumor immune cells that might be present are often impaired in the TME.

Thus, effective immunotherapy requires a combination of potent stimulation of anti-tumor immune responses and, additionally, manipulation of the immunosuppressive environment to prevent tumor escape. Therefore, elucidating the mechanisms of responsiveness or refractoriness and the molecular determinants thereof is required to improve cancer immunotherapy.

The objective of our department is to demonstrate the feasibility of an immunological data-guided personalized adaptive approach to immunotherapy, whereby immunomodulatory strategies are tailored to the patient's specific TME.

Teaching activities

Research guidance in molecular immunology is provided to postgraduate students. Because knowledge

and techniques for evaluation of immune response are important for clinicians and medical researchers, we also provide many opportunities to postgraduate students to learn how to analyze *in vivo* immune responses through experiments using animal models and by the immunological monitoring of the patients themselves in clinical research.

Research activities

1) Evaluation of tumor-immune interaction.

Immunotherapy with immune checkpoint inhibitors (ICIs) has completely changed the therapeutic landscape for many types of solid tumors. Several combinations of immunotherapy with chemotherapy, molecular targeted drugs, or combinations of different ICIs are now approved for the first-line treatment of various cancers. However, not all types of cancer respond equally well to ICIs, and even in responsive cancers, only a subset of patients experiences durable responses and favorable long-term outcomes. This is because primary and acquired resistance occurs in a considerable proportion of patients across different cancer types.

Therefore, it is crucial to establish reliable predictive biomarkers to distinguish ICI responders from non-responders, who may suffer unnecessary costs and toxicities, and to identify candidates for rational combination therapies. Currently, tumor mutational burden and PD-L1 expression are the two major

variables used as biomarkers that have been validated in phase III clinical trials. Additionally, several other factors associated with response or resistance to ICIs across cancer types have been proposed as biomarkers, based on molecular profiling of cancers treated with different immunotherapies. These include an immune-inflamed phenotype, expression of T cell signaling pathway genes such as IFN γ , microsatellite instability, somatic copy-number alterations, HLA class I diversity, T cell repertoire clonality change, WNT- β -catenin signaling, TGF β expression and even commensal microbiota.

However, as single biomarkers, none of the above is sufficient to identify individual patients who will likely benefit from immunotherapy. Unlike conventional cancer therapies, immunotherapies, including ICIs, do not directly target tumor cells; instead, they affect tumor cells through the patient's immune system or the tumor microenvironment (TME). Therefore, the different components that affect tumor-immune interactions need to be taken into account when developing predictive biomarkers for immunotherapy. Comprehensive analysis of multiple different functional pathways and molecular networks that reveal integrated mechanisms of tumor-immune interactions are crucial for this purpose. General and local cancer immunity status in each patient needs to be taken into consideration.

To this end, Blank et al. proposed the concept of the cancer immunogram that integrates multiparameter biomarkers to visualize the immunological status of an individual patient. We have applied this concept to lung cancer patients and developed an immunogram reflecting the cancer-immunity cycle. Since then, van Dijk et al. have reported an immunogram informative specifically for urothelial cancer patients. Although immunograms may be useful for visualizing the landscape of the tumor microenvironment and the compromised steps of anti-tumor immunity in each patient, both Blank et al. and van Dijk et al. had only theorized that they could be useful to patients but had not tested the concept in clinical practice. In contrast, we analyzed real-world lung cancer patient data to generate immunograms with potential applications for personalized immunotherapy. We utilized RNA-Seq

data from the TCGA cohort as a standard and set up a scoring scale to quantify parameters incorporated in the immunogram. We propose a novel versatile scoring method for constructing such individual immunograms.

2) To develop combinatorial and personalized immunotherapy.

Immune profiling, including bulk transcriptome assays with microarrays or bulk RNA-Seq as well as fluorescence-based flow cytometry, contributes valuable insights into the mechanisms behind tumor-immune cell interactions and can uncover mechanisms and biomarkers for prediction of therapeutic responses. Recently, high-dimensional technologies such as scRNA-Seq and cytometry by time of flight (CyTOF) are being increasingly employed for immune profiling in cancer in order to detect rare immune subsets and dissect phenotypic and functional heterogeneity. Using these new technologies, deep immune phenotyping at the single-cell level is possible in the individual patient. Deep phenotyping of the TME of each patient will be a useful guide to potential individual target molecules or cells and to determining the therapeutic strategies to be adapted for each patient.

The future of immunotherapy will be combinatorial and personalized treatments adapted to each patient's cancer-immune interactions in the TME. Clearly, instigating this type of personalized therapy will be challenging for many reasons, not the least of which will be the high cost and labor-intensive nature. However, it is to be expected that technical advances will overcome some of these difficulties. Fortunately, the cost of NGS is decreasing every year, and the development of a cost-effective targeted scRNA-Seq platform using our original VFAC will hopefully contribute to this.

To demonstrate the feasibility of an immunological data-guided personalized adaptive approach to immunotherapy, whereby immunomodulatory strategies are tailored to the patient's specific TME, we utilized tumor-bearing mice model. The TME of growing tumors was immunologically assessed and the animals were treated based on those results. Using

scRNA-Seq, but not bulk RNA-Seq, it was possible to determine the molecules in the tumors that were involved in generating an immunosuppressive microenvironment. Tumors currently considered non-responsive to immune checkpoint therapy might be convertible to responders by elucidating and regulating the complicated network of cancer cells and immune cells in the individual patient TME.

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Presentation at International conference

- 1) 2020/7/23. AACR2020 VIRTUAL ANNUALMEETING II Virtual Minisymposium. Kazuhiro Kakimi. Autologous $\gamma\delta$ T cell therapy for treatment-refractory non-small-cell lung cancer: An open-label, single-arm, multicenter, phase II study
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combined with MHC ligandome profiling,

- 5) 2020/8/17-19. Keystone Symposia: eSymposia. Koji Nagaoka, Masataka Shirai, Kiyomi Taniguchi, Akihiro Hosoi, Changbo Sun, Yukari Kobayashi and Kazuhiro Kakimi. Deep-immunophenotyping at the single-cell level identifies a combination of anti-IL-17 and checkpoint blockade as an effective treatment in a preclinical model of data-guided personalized immunotherapy.

Department of Ubiquitous Preventive Medicine

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Introduction and Organization

As an official department in the Graduate School of Medicine of the University of Tokyo, the Department of Ubiquitous Preventive Medicine was established in August 1st, 2007, with a donation from three pharmaceutical companies, Toa-Eiyo Ltd., Shionogi & Co., Ltd. and NEC Corporation to the University. Its predecessor is the Clinical Bio-Informatics Research Unit, which was established in 2002 as a government-funded program (Bio-Informatics Training Program supported by the Ministry of Education, Culture, Sports, Science and Technology [MEXT] through Special Coordination Funds for Promoting Science and Technology). When the Clinical Bio-Informatics Research Unit completed its program tenure in 2007, its academic services were succeeded by our department and the Department of Clinical Epidemiology and Systems, both affiliated with the Department of Cardiovascular Medicine in the Graduate School of Medicine of the University of Tokyo.

Our department provides clinical as well as academic support for the Department of Epidemiology and Preventive Medicine, which was established in 2007 within the University of Tokyo Hospital. In collaboration with our department, the Department of Clinical Epidemiology and Systems also support the management of the Department of Epidemiology and Preventive Medicine.

Research Activities

Our goal is to create diagnostic and therapeutic basis for prevention and early detection of cardiovascular diseases by utilizing advanced techniques of biochemistry and molecular pharmacology. We especially focus on the discovery of bioactive molecules and diagnostic biomarkers in order to promote translational research, which connects basic scientific findings to tangible clinical application.

One of our achievements is the establishment of a novel technique for detecting post-translational modification and degradation of B-type natriuretic peptide, one of the most important biomarkers in cardiovascular pathologies such as ischemic heart disease and heart failure. This unique technique was developed in collaboration with Shimadzu Corporation. We have already confirmed and published its utility in clinical practice (Clin Chem, in press), further, issued press-release from the University of Tokyo Hospital.

In addition to the development of diagnostic techniques, we have also established several screening systems towards the discovery of bioactive substances that are involved in the pathogenesis of cardiovascular diseases. Utilizing these newly developed systems, we will screen tissue extracts and a small-molecule compound library to identify novel bioactive molecules.

In this way, Ubiquitous Preventive Medicine is an applied science, based on which a comprehensive system is to be developed in an effort to promote preventive medicine for health promotion.

Clinical activities

The Department of Ubiquitous Preventive Medicine is involved in the management of the Department of Epidemiology and Preventive Medicine in the University of Tokyo Hospital and provides clinical as well as academic support for the department.

Teaching activities

The Department of Ubiquitous Preventive Medicine offers education and research supervision to graduate students and post-doctoral fellows in the affiliate Department of Cardiovascular Medicine.

Publications

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Introduction and Organization

Why we discuss Clinical Data Management (CDM)?

The reason why the concept of CDM is important has not been fully discussed and educated in Japan. Our department was established to answer this question.

The Department of Clinical Trial Data Management was established in 2007 and carried out educational and research activities on CDM in collaboration with The Department of Biostatistics, The Clinical Research Support Center and Department of Health Communication in University of Tokyo.

As compared to the situation of CDM in the United States and Europe, technical aspects (data collection, entry, check...) have been mainly focused in Japan but the essence of CDM is to ensure quality of clinical data to appropriate level for fair and scientific evaluation. This has not been recognized in many educational activities. CDM should be defined as a

technical system to conduct clinical trials scientifically, ethically and efficiently and to draw correct conclusion and also as a research discipline with theory and practice that applies statistics, quality control and clinical knowledge. It can optimize the whole clinical trial process, keep the level of data quality appropriately and calculate the trial cost.

One of our missions is to promote researches on CDM aimed at improving the quality of clinical trials. The other is to provide training for data managers with the new education system which can look around all the clinical trial process to adapt rapid change of medical environment and recent increase of e-clinical trials in the world.

Teaching activities

1. Development of systematic educational programs of CDM and holding of seminars, which include;

- Design of clinical trials
- CDM
- Risk-based Monitoring
- Patient-reported Outcome
- Mobile Health
- Safety information and PMS
- Translational research methodology

2. Acceptance of clinical trial staffs from other sites, that is, conducting an on-the-job training (OJT)
3. Support to clinical researchers, especially those in the University of Tokyo Hospital, in collaboration with the Clinical Research Support Center and the Department of Clinical Epidemiology and Systems;
 - Consultation works on medical statistics and research methodology
 - Functioning as a data center and staffs participate in projects as biostatisticians or clinical data managers.

Research activities

In addition to activities described above, we are conducting the research on methodology of Risk-based monitoring, mobile Health (mHealth) and developing ePRO in collaboration with other universities, pharmaceutical industries, CRO and vendors.

We are also supporting several clinical studies which are conducted in the University of Tokyo Hospital. Moreover, we also have collaborative works outside of University of Tokyo Hospital for several clinical researches.

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Social Cooperation Program

Department of Advanced Nursing Technology

Project Associate Professor

Ryoko Murayama, Ph.D., R.N.M.

Project Assistant Professor

Mari Abe, MHS, R.N.

Visiting Researcher

Hidenori Tanabe, MS.

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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.

The primary master thesis in 2020 was titled "Changes in the blood vessel and subcutaneous tissue of peripheral intravenous catheter placement sites: An observational study using ultrasonography"

We were in charge of lectures on nursing translational research at the seminar hosted by GNRC for post-doctoral fellows and other researchers. (The 8th 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 will be 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 are also ongoing 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 are being conducted in collaboration with nurses at the University of Tokyo Hospital.

We offer lectures and consultations on research matters and provide guidance on article writing to promote nursing research in the clinical setting. We are 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 2020

- 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

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Department of Imaging Nursing Science

Project Associate Professor

Nao Tamai, Ph.D

Project Lecturer

Masaru Matsumoto, Ph.D

Project Assistant Professor

Yuka Miura, Ph.D

Collaborative Researchers

Mayumi Handa and Mikihiro Karube

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

Organization history and overview

The Department of Imaging Nursing Science was founded as part of the Corporate Sponsored Research Programs offered by the Graduate School of Medicine, The University of Tokyo, in April 2017. It aims to realize “a safe, secure, and comfortable medical care experience” through visualized nursing technology. The department conducts translational research through surveys on actual nursing care conditions based on imaging technology and propose nursing techniques and their evaluation, with the goal of developing care systems and applying these in clinical settings.

Specific plans include developing (1) an ultrasound technology support system for nursing care, (2) a remote support system using imaging technology to assist nursing care, and (3) innovative technologies using new imaging techniques in nursing.

This Social Cooperation Program was established with the cooperation of FUJIFILM Corp. and with the Department of Gerontological Nursing / Wound Care Management as partner departments aiming to find solutions to these challenges and to further the progress in nursing technologies. It aspires to establish imaging nursing technologies in clinical nursing

settings in Japan, as a forerunner in shifting towards a globally unprecedented super-aging society, and to become the first transmitter of new discoveries to the world.

Department members are Project Associate Professor Nao Tamai, Project Lecturer Masaru Matsumoto, Project Assistant Professor Yuka Mirura, and Visiting Researchers Mayumi Handa and Mikihiro Karube (FUJIFILM Corp.). The Project Associate Professor concurrently served as a member at a visualized nursing field of Division of Care Innovation, the Graduate School of Medicine, Global Nursing Research Center and now strives to establish and disseminate imaging nursing skills in nursing research.

Education

In 2020, we provided the following lectures for undergraduate and postgraduate students.

- a) Bioengineering Nursing (S2 in 4th yr.)
- b) Practicum in Human Health Support (W in 2nd yr.)
- c) Gerontological Nursing Practice (A2 in 4th yr.)
- d) Special Lecture in Gerontological Nursing I (S1)
- e) Special Lecture in Wound Care Nursing I (S2)

f) Special Lecture in Wound Care Nursing II (A)

We have provided cooperation and guidance to undergraduate students in the Department of Health Science and graduate students in the Department of Gerontological Nursing and Wound Care Management for their research plans through seminars and practical training.

Through external lectures and workshops to increase awareness, we have held lectures on skin and elimination care at levels equivalent to curricula for Certified Nurses in Wound, Ostomy and Continence Nursing course at the Nurse Training Center of the Kyoto Tachibana University. We have also held lectures on training for nurse-designated procedures in the Nursing Training School of the Japanese Nursing Association.

At the nursing science and engineering introductory seminar, hosted by the Global Nursing Research Center of the Graduate School of Medicine, we lectured to many nursing researchers and clinical nurses at a webinar on imaging nursing skills, especially those which were challenged in clinical settings.

Research

This course seeks to develop nursing assessment skills using ultrasonography and to promote research in imaging nursing that directly contributes to clinical settings. We are developing a versatile portable ultrasound device that is ultralight-weight, produces high image quality, and operates on a wide range of frequencies. Furthermore, a nursing assessment coaching software is being developed using imaging analysis, which does not require special techniques, to support assessment by nurses.

Specifically, we undertook research and development on the following topics:

- 1) Supporting swallowing care: Improvement of pharyngeal-residual-observation method of pyriform sinus.
- 2) Supporting urination care: Standardization of bladder-urine-volume-measurement method in the standing and sitting position using ultrasonic device and examination of a method to identify urinary tract infection in older adults.
- 3) Supporting defecation care: Clinical implementation of an educational program on evaluation of stool retention using ultrasonic equipment, construction and evaluation of ICT system, development of stool retention evaluation method for ultrasonic movies by AI.
- 4) Supporting pressure injury care: development of educational programs using ultrasonic devices and development of methods for detecting deep tissue injuries by AI.

With these research activities, we have received the following awards:

- ・第8回看護理工学会 学会賞（2020年10月）. Morphological characteristics of skin tears to estimate the etiology-related external forces that cause skin tears in an elderly population. Koyano Y, Nakagami G, Tamai N, Sugama J, Sanada H. *Journal of Nursing Science and Engineering*. 2020;7:68-78.
- ・第40回日本看護科学学会学術集会 JANS40 大会賞（2020年12月）. 末梢静脈点滴トラブルを防ぐ為の超音波画像を用いた AI によるケアリコメンデーションシステムの開発. 高橋 聡明, 村山陵子, 仲上豪二朗, 阿部麻里, 松本 勝, 真田弘美. 第40回日本看護科学学会学術集会抄録集. 2020;61.

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Department of Healthcare Quality Assessment

Project Professor

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Clerical Staff (Secretary)

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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 more than 5,300 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.

Clinical databases like NCD are the core components of quality improvement initiative in many health care services such as in the field of thoracic surgery. 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 number of clinical researches, conducted in collaboration with the professional societies, has come out based on detailed analyses of

various registry data collected by NCD. Also, in collaboration with Pharmaceuticals and Medical Devices Agency as well as device manufacturers, new registries have worked on academia-government-industry collaboration projects using NCD registry data. One example is the research project based on the registry for transcatheter valve therapy which also supported the manufacturers' post-marketing surveillance activities. HQA has also been involved in international research collaborations with major registries abroad, including American College of Surgeon's NSQIP, Asian Cardiac Database and The Society of Thoracic Surgeons National Database, aiming to participate in quality improvement activities in different regions of the world.

Select Publications

- Okamura A, Yamamoto H, Watanabe M, Miyata H, Kanaji S, Kamiya K, et al. Association between Preoperative HbA1c Levels and Complications after Esophagectomy: Analysis of 15 801 Esophagectomies from the National Clinical Database in Japan. *Ann Surg.* 2020; doi: 10.1097/SLA.0000000000004547 Epub.
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- Saito A, Kumamaru H, Miyata H, Motomura N. Device use for proximal anastomosis on ascending aorta in off-pump coronary artery bypass grafting. *Ann Thorac Surg.* 2020; 111:1909-1915.
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- 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.* 2020; doi: 10.1097/SLA.0000000000003804. Epub Jan 21.

Department of Tissue Stem Cells and Life Dentistry

Project Professor

Makoto Komura, M.D., Ph.D.

Project Lecturer (Jan, 2021-)

Yukio Asano, D.V.M., Ph.D.

Project Assistant Professor (April, 2020-December, 2020)

Ryoko Inaki, D.D.S., Ph.D.

Homepage <http://plaza.umin.ac.jp/~tsc-lds/manage.html>

Introduction and Organization

A social cooperation course, The Department of Tissue Stem Cells and Life Dentistry was 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 (bio sheet / bio tube) 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 Assistant Professor (April-December, 2020) and now assisted by a Project Lecturer (January, 2021-).

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 in the upcoming year.

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.

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

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Department of Skincare Science

Project Associate Professor

Takeo Minematsu, Ph.D.

Project Lecturer

Misako Dai, R.N., Ph.D.

Homepage <http://skincarescience.m.u-tokyo.ac.jp/index-e.html>

Introduction and Organization

The Department of Skincare Science was established in the Graduate School of Medicine with funding from Saraya Co., Ltd. on February 1st, 2017. The global aim of our department is to develop new nursing technologies to evaluate and improve the physiological condition of vulnerable skin due to aging and disease.

The department is currently headed by a Project Associate Professor and assisted by a Project Lecturer.

Teaching activities

In 2019, we gave the following lectures to undergraduate, master and Ph.D. students:

- a) Nursing Science and Engineering (S2 in 4th yr.)
- b) Gerontological Nursing I (S1 in graduate students)
- c) Wound Care Management I (S2 in graduate students)
- d) Wound Care Management II (S2 in graduate students)

We supervised graduate students within the Department of Skincare Science and the Department of Gerontological Nursing/Wound Care Management on individual research projects, research planning and training work.

In 2020, Ph.D. and master's courses involved the following research themes:

Ph.D.: "Development of the measurement of taurine concentration by the skin blotting: A non-invasive identifying method for chronic dehydration of vulnerable older people in home care setting"

Master's: "Identification of microRNAs responsive to

share loading in rat skin"

We gave lectures on the suitability of physiological and molecular biological approaches based on analytical and critical thinking to nursing researchers, nurses, and graduate students in the 8th Nursing Science and Engineering Seminar, which was held by the Global Nursing Research Center, Graduate School of Medicine, The University of Tokyo.

Research activities

The skin is the only organ that can be directly seen and touched physically on a daily basis. Any abnormalities to the skin cause pain and itching, which significantly impair patients' Quality of Life (QoL). Therefore, our research focuses on skin assessment and skincare to maintain skin integrity and promote a healthy life for patients.

In particular, we are working to establish and disseminate the research methodology of "biological nursing" which aims to biologically elucidate the causes and developmental mechanisms of disordered skin conditions and discomforts, and to identify new care targets.

Skin blotting and wound blotting represent our care innovations through biological nursing studies. These are simple and non-invasive technologies to assess the physiological status of the skin and wounds. Since February 2017, we have been closely working with Saraya Co., Ltd., to develop new nursing technologies to apply wound blotting in clinical settings. After its development in 2018, this new product has been applied in many facilities. In addition to this effort, we have also contributed to the 2020 Tokyo Paralympic

Games through pressure ulcer care for wheelchair athletes.

The following are the research topics of our department in 2020:

- Development of non-invasive skin assessment using the skin blotting to:
 - Identify chronic dehydration
 - Distinguish Category I pressure injuries
 - Identify deep tissue damage on the buttocks of wheelchair athletes
 - Predict skin tear development
- Development of wound assessment using wound blotting and investigation of its practical applications to:
 - Identify latent wound infection
 - Improve biofilm detection
- Pressure injury care in wheelchair athletes
 - Development of wheelchair cushions for daily living and performance
 - Prevention of pressure injury on buttocks by vibration
- Lymphoedema care
 - Identification of ultrasonographic features of subcutaneous tissue related to cellulitis recurrence
 - Identification of biomarkers related to cellulitis recurrence
- Scalp care of patients who have undergone anti-cancer drug therapy
 - Structural and physiological alterations in scalp due to anti-cancer drug therapy
 - Effectiveness of medical wigs made from novel materials

Our research has been internationally recognized in the form of several awards, including:

- Bronze Award of IAUD International Design Award. 2020/12/18.
- International Lymphoedema Framework Japan 10th Anniversary Award. 2020/11/26.

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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 three 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 2018, 6.5 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 patients with diabetes

Discontinuation of diabetes care is associated with increased rate of complications and mortality. One of the limitations in the previous studies is selection bias, as the patients mostly voluntarily participated in the studies so were more motivated than the average patients. In order to identify predictors of discontinuation in patients with diabetes in real-world data, we have analyzed the JMDC database in collaboration with the Department of Clinical Epidemiology and Health Economics (Professor Hideo Yasunaga).

3) Research on diabetes and cancer

Patients with diabetes have higher risks of developing such diseases as cardiovascular diseases, cerebrovascular diseases, kidney diseases and cancer. While improved glycemic controls is associated with a reduced risk for vascular diseases and kidney diseases, association between glycemic control and cancer risk is unclear. In order to investigate this issue, we are analyzing data of patients with diabetes in a 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.

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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.

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 the School of Pharmaceutical Sciences, as well as medical student belonging to the Medical Scientist Training Program. In addition, TH has given a lecture on "Special Course for Clinical Pharmacy" 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 A β dynamics in the brain Amyloid β peptide (A β), 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, A β is readily cleared by proteolytic degradation or transported outside the brains. However, A β that escaped from the clearance starts to aggregate and deposit forming amyloid fibrils. Thus, the elucidation of the A β 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 A β 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 A β 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 A β and evaluate the following A β deposition (Hori Y, et al., *J. Biol. Chem.*, 2015), we have identified a >200 kDa high molecular weight A β oligomer species in the soluble fractions of brains of APP transgenic mice and AD brains (Hashimoto T, Soc for Neuroscience meeting 2017). We will further identify A β species that are involved in the A β dynamics in the brain, including those specifically involved in deposition or toxicity of A β .

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 (ϵ 2, ϵ 3, ϵ 4), 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 ϵ 4 allele is ~8-10% in normal population, whereas it is elevated to >30-40% in AD. Thus, ApoE ϵ 4 is a strong genetic risk factor of AD, although the mechanism whereby ApoE ϵ 4 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 A β dynamics in the brain. This will lead us to the intervention into the effect of apoE isoforms on A β , toward the goal of AD prevention. In 2017, we have found a significant decrease in A β deposition in the brains of human apoE3 KI/APP transgenic mice. In 2018, we have also found that apoE3 reduced the deposition of A β compared with murine apoE using in

vivo seeding technique. We also found that the A β levels in the interstitial fluids of human apoE3 KI/APP transgenic mice are similar to those in APP transgenic mice by in vivo microdialysis method. We also have established a method to monitor the interaction between A β 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 A β .

③ Establishment of a novel AD model using three-dimensional culture system for the development of prevention methods targeting brain A β 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 A β deposition and A β -dependent neurotoxicity reminiscent to that in AD brains. In 2018, we found the phosphorylation of tau by the overproduction of E22G mutant A β in the ReNcell-VM neurons. We will use this system for the development of anti-dementia drugs targeting A β 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 Alzheimer's disease (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 A β 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 A β clearance in the brain caused by HFD feeding.

In APP Tg mice lacking IRS-2, which plays an important role in signal transduction as a substrate for insulin and IGF-1 receptors, amyloid accumulation in the brain was markedly suppressed, despite the fact that the mice exhibit systemic insulin resistance and develop diabetes. 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. We are now focusing on ER stress as a molecular mechanism by which HFD feeding promotes the formation of amyloid plaques, and are conducting in vivo studies.

In addition, the mechanism by which IRS-2 deficiency has a protective effect on A β accumulation has not yet been elucidated. Deficiency of not only IRS-2 but also insulin receptor and IGF-1 receptor suppresses A β 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.

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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 maintenance of health services particularly in the aging 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.

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 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 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 disease, including respiratory disease.
- 2) Outcomes and cost effectiveness in both western medicine and eastern medicine in Japan.
- 3) Impact of super aging society on population dynamics and demand of health services.
- 4) Efficient distribution of medical staffs, medical institutions and armamentarium.

The followings are the examples of studies

conducted in 2020.

1) High-dose versus low-dose intravenous immunoglobulin for treatment of children with Kawasaki disease weighing 25 kg or more

Little is known whether 2 g/kg IVIG is necessary for older children with Kawasaki Disease (KD), because they could have more complications and financial burden. The purpose of this study was to compare outcomes between high and low-dose IVIG in KD children with higher body weight (25 kg or more), using a national inpatient database in Japan from 2010 to 2017.

We identified those receiving 2 g/kg and 1g/kg IVIG as an initial treatment. Outcomes included the proportions of coronary artery abnormalities (CAA) formation, IVIG resistance, adverse effects, length of stay, and medical costs. A propensity-score matching analysis was conducted to compare the outcomes between the groups.

We identified 1332 patients with KD and created 4:1 propensity-score matched pairs between high and low-dose IVIG groups. There were no significant differences in the proportions of CAA (5.3% vs. 4.1%; $p=0.587$), IVIG resistance and length of stay. Medical costs were significantly higher in the high-dose group than low-dose group ($p<0.001$).

No significant difference was shown between the high and low-dose IVIG groups in the proportions of outcomes, while medical costs were higher in the high-dose group. Further studies are needed to ascertain the appropriate IVIG dose in older patients with KD.

2) Association between mandatory health examination attendance and diabetes treatment initiation among employees being treated for hypertension

It is unclear whether mandatory health examination is effective for employees who are already being treated for chronic diseases. We focused on patients being treated for hypertension and evaluated the association between employer-based health examination attendance and diabetes treatment initiation.

Using a database that stores health insurance claims and health examination results of subscribers enrolled in society-managed health insurance plans in Japan, we identified employees aged 40–59 years who were being treated for hypertension when starting diabetes

treatment from April 2012 to December 2016. A case-crossover analysis was conducted using 90, 180, and 270 days prior to diabetes treatment initiation as reference points and 90 days after the mandatory health examination as the exposure period. We conducted a subgroup analysis by hemoglobin A1c (HbA1c) level and frequency of outpatient blood glucose testing before the mandatory health examination.

We identified 1464 individuals starting treatment for diabetes while on antihypertensive drugs. The overall odds ratio for starting diabetes treatment within 90 days of the health examination was 1.89 (95% confidence interval: 1.70–2.10). The subgroup analysis showed that this odds ratio increased as HbA1c level increased and as blood glucose testing frequency decreased.

Among employees starting treatment for diabetes while being treated for hypertension, employer-based mandatory health examination attendance was associated with initiation of diabetes treatment. The health examinations may be functioning as a complement to screening in outpatient settings.

3) Inhaled corticosteroid withdrawal may improve outcomes in elderly patients hospitalized for COPD exacerbation: A nationwide database study

Inhaled corticosteroids (ICS) is used for advanced-stage COPD. However, in patients with COPD exacerbation, withdrawal of ICS can often be unavoidable. This study aimed to evaluate the association between ICS withdrawal and outcomes in elderly patients with COPD exacerbation.

We conducted a retrospective cohort study using Japanese Diagnosis Procedure Combination inpatient and outpatient database from July 2010 to March 2016. We identified patients aged ≥ 65 years who were hospitalized for COPD exacerbation. Re-hospitalization for COPD exacerbation or death, frequency of antimicrobials or anti-flu medicine prescribed within one year after discharge, and frequency of oral corticosteroids prescription after discharge were compared between patients with withdrawal and continuation (control) group of ICS, using propensity score analyses.

Among 23,047 eligible patients, the numbers of those with ICS withdrawal and continuation were 971 and 2,764, respectively. Hazard ratios (95%

confidence intervals) of re-hospitalization for COPD exacerbation or death for the ICS withdrawal group (with reference to the control group) was 0.68 (0.54 to 0.84) in the 1-to-2 propensity score matching and 0.71 (0.56 to 0.90) in the stabilized inverse probability of treatment weighting. Frequency of antimicrobials or anti-flu medicine prescription within one year was significantly less in the ICS withdrawal group than in the control group, whereas frequency of oral corticosteroids prescription within 30 days as well as within one year was not significantly different between the two groups.

In elderly patients, ICS withdrawal after COPD exacerbation was significantly associated with reduction in re-hospitalization or death. ICS withdrawal may be a feasible treatment option in elderly patients with COPD exacerbation.

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.

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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, glycation stress, oxidative stress) in CKD; and using the findings obtained to establish new CKD treatment strategies.
- 2) Clarifying the mechanism of functional change in renal erythropoietin (EPO)-producing cells, along with the mechanisms of CKD progression and identification of the mechanism of development and progress of renal anemia.
- 3) Clarifying the impact of kidney aging on CKD progression in super-aging society
- 4) Identifying factors in the exacerbation of CKD in patients with diabetes, and developing diagnostic and therapeutic drugs targeting such factors.
- 5) Pathophysiology of uremic toxins on organ crosstalk and impact of uremia management in CKD
- 6) Elucidating the neuro-immune axis in kidney injury
- 7) Role of ADP-ribosyl cyclase (Bst1, CD38) in renal injury

Research Funds (PI)

- Japan Society for the Promotion of Science, Grants-in-Aid for Scientific Research
18H02727 (to **Reiko Inagi**, Mechanisms of organelle cross talk disorder and failure of organ homeostasis in aging and disease),
18H06192 (to **Tsuyoshi Inoue**, The mechanism of immune cell activation in the cholinergic anti-inflammatory pathway)
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)
PRIME 19gm6210013h0001 (to **Tsuyoshi Inoue**, Elucidation of cell interaction mechanism in suppression of chronic kidney disease progression through nervous and immune systems)
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 **Tsuyoshi Inoue**, Suppressive mechanism of atherosclerosis progression by vagus nerve stimulation)
- The Kidney Foundation, Japan, Grant for pathophysiological research conference in chronic kidney disease (to **Tsuyoshi Inoue**, Elucidation of erythropoietin production regulation mechanism by vagus nerve)

- Takeda Science Foundation, Medical Research Grant (to **Tsuyoshi Inoue**, Elucidation of new anti-inflammatory and organ protection mechanisms controlled by autonomic nervous system)
- Mochida Memorial Foundation for Medical and Pharmaceutical Research, Research Grant (to **Tsuyoshi Inoue**, Elucidation of the mechanism of macrophage anti-inflammatory effect by sympathetic and parasympathetic stimulation)
- Astellas Foundation for Research on Metabolic Disorders, Research Grant (to **Tsuyoshi Inoue**, Anti-inflammatory mechanism of macrophages by autonomic nerve stimulation)
- Suzuken Memorial Foundation, Research Grant (to **Tsuyoshi Inoue**, Study on therapeutic effect of autonomic nerve stimulation in kidney disease)

Awards

Dr. Hiroshi Maekawa received the Young Investigator Award at the 63rd Conference of Japanese Society of Nephrology.

Dr. Sho Hasegawa received the CKD Frontier Award at the 9th Chronic Kidney Disease Frontier.

Dr. Sho Hasegawa received the Young Investigator Award at the 18th Annual Meeting of Asian Pacific Congress of Nephrology.

Dr. Sho Hasegawa received the Advances in Research Conference Trainee Support Grant of American Society of Nephrology.

Dr. Sho Hasegawa received the CKD Frontier Award at the 10th Chronic Kidney Disease Frontier.

Dr. Sho Hasegawa received the Young Investigator Award at the 24th Annual Meeting of the Society of Cardiovascular Endocrinology and Metabolism

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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 one technical assistants.

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

Applying 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.

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Department of Preventive Medicine for Locomotive Organ Disorders

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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, ALCARE Co., Ltd. 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.

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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 2020, 205,277 outpatient blood sampling were performed in this section. Furthermore, 239,098 urine samples were examined.

The 2nd Section

This section deals with clinical biochemistry and immuno-serology tests. In 2020, 5,077,465 serum

enzyme tests (such as AST and ALT), and 512,042 immunological tests were performed.

The 3rd Section

This section deals with laboratory hematology and DM-related tests, and gene analysis tests. In 2020, 1,087,307 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 2020, 37,979 ECG, 16,273 pulmonary function tests, and 9,068 EEG were performed.

The 5th Section

This section deals with ultrasonography. In 2020, 10,123 echocardiography tests, 11,960 abdominal echography tests, and 9,068 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.

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.

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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, 9,921, 9,944, 10,394, 10,170, 10,752, 11,235, 11,150, 10,960, 11,161, 11,014, 11,124, 11,323 and 9,945 (under the circumstance of Covid-19 pandemic) operations were performed in 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018, 2019 and 2020 fiscal year, respectively. The number of operations in 2019 fiscal year counts for approximately 1.8 times comparing to that in 2001.

These days more and more patients undergo endoscopic surgery such as laparoscopy/thoracoscopy

assisted operation. There is also an apparent increase in the number of patients who are at high risk with critical morbidity or carrier of the particular types of pathogens such as tuberculosis, MRSA, *Pseudomonas aeruginosa*, HBV, HCV and HIV.

Clinical Activities

All operations of in-patients are performed in 23 ORs and Day Surgery room at the surgical center. Computer system has been utilized to handle the information on operation. In May 1999, the on-line system was introduced to order the elective and urgent/emergent operations through the computer terminal in the wards. The input of postoperative patient information started from March 2000. This system also enabled the medical staff to know the availability of the ORs of the next day. From November in 2000, the medical staff can see the operation schedule through the hospital computer network.

The present status of the operation process began to be seen through the computer monitor from May 1997. The photographs of surgical sites, resected organs and live video image began to be delivered to the clinical departments from February 1997.

Hospital logistics system were totally replaced to improve material flow of hospital in October 2001, when supply processing and distribution (SPD) department was established and started its practice. In the surgical center, this SPD system has been available since September in 2002.

Recently, the number of complicated and long surgical procedures using advanced technology has dramatically increased. In addition, more and more patients tend to undergo surgery using artificial implant, joint prosthesis or intraocular lenses. Those operations include organ transplantation, microvascular surgery, cardiovascular surgery, minimally invasive surgery and navigation-guided orthopedic/neurosurgical surgery and stent grafting for the abdominal or thoracic aortic aneurysms. Organ transplantation and intraoperative three-dimensional echo-guided surgery are also frequently performed. Minimally invasive surgery is another recent trend of the operation. Those include endovascular treatment for heart anomalies such as ASD and VSD. More recently, the robotic surgery has started at the surgical center.

Healthcare-Associated infections (HAIs) are critical issues in the surgical center. It is essential to educate staffs how to prevent HAIs and occupational infections. As the number of operations associated with emerging or re-emerging infectious diseases such as HIV and tuberculosis has increased, all healthcare staff are required to adhere to the principles of standard and/or transmission-based precautions also in the surgical center.

Teaching Activities

The following lectures or seminar are given to the undergraduate and postgraduate medical students: aseptic techniques, sterilization/disinfection methods, prevention of perioperative infections, humoral and cellular responses to trauma and shock, training of scrubbing and gown techniques. The curriculum is updated each year. Introductory course for disinfection, sterilization and preservation of surgical instruments and medical devices was added in the training courses in 1998, which gained more interest and popularity among many students.

In the surgical center, the innovative surgical instruments and medical devices are introduced to perform highly advanced operations such as in the navigation surgery, transplantation surgery, cardiovascular surgery and robotic surgery. As a result, the education related to the assist for those surgical procedure has become most important activities in the surgical center. The lectures of advanced technologies are in the curriculum for the surgeons, the nursing staff and clinical engineers so that they can understand how to use them in a proper way.

Lectures for the nursing staff consist of a freshman course and an advanced course. The freshman course is a basic training course for scrub nurses and circulating nurses. It consists of lectures of aseptic techniques, decontamination/sterilization methods, prevention of perioperative infections, and on-site training of scrubbing and gown techniques as well as aseptic preparation of surgical instruments in the OR. An advanced course is prepared to the experienced nurses as well. The purpose of this course is to upgrade their perioperative nursing skills so that they can demonstrate full nursing skills even in the complicated and long operations such as transplant surgery, open-

heart surgery neurosurgery and robotic surgery.

There is also a training course to medical engineers and students of biomedical engineers. This training course consists of introduction on the medical devices and electronic instruments, precautions of accidental troubles in handling surgical instruments/medical devices, development of new surgical instruments/medical devices, cardiopulmonary bypass techniques and illumination techniques in the operating fields. The contents of this course are summarized in the manual for the nursing staff and contribute to decrease the frequency of incident associated with surgical instruments and medical devices.

The on-the-job training are given to the non-nursing staff including technical officials and part-time employees since they start their careers at the surgical center. They are given lectures on aseptic techniques, sterilization/disinfection methods, prevention of perioperative infections, and maintenance of reusable surgical instruments such as forceps, scissors and clamps. These subjects are stated and summarized in the manual. Lectures are also given to the senior technical officers and part-time employees to promote their technical knowledge and skills.

13) Nutritional management of perioperative patients

14) Others

Research Activities

- 1) Safe surgery and risk management in the OR
- 2) Improvement of cost-effectiveness in the surgical treatment
- 3) Development of central monitoring system using IT technology
- 4) Introduction of robotic surgery
- 5) Efficient use of human resources
- 6) Introduction of advanced surgical procedure including microscopy surgery and laparoscopy
- 7) Management of equipment of endoscopy-assisted surgery
- 8) Centralization of the live video images of the surgical field
- 9) Management of surgical instruments using unique device identification (UDI)
- 10) Perioperative infection control and prevention related to the sterilization
- 11) Maintenance of the surgical environment in the OR
- 12) Maintenance and management of surgical equipment

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Introduction and Organization

In the Department of Clinical Radiology, clinical services on Diagnostic Radiology (imaging and intervention), Radiation Oncology (radiotherapy), Nuclear Medicine, and the Radiation Safety Control System are provided in cooperation with radiology technologists and nurses. Present constituent members are three medical doctors, 75 radiological technicians, and one technical official of the radiation control. In addition, the Department of Radiology staff members (teachers, graduate school students, medical staff, and clinical trainees) join this. In addition, the doctors of other departments and the nurses cooperate and are also engaged in clinical radiology activities.

Department of Clinical Radiology is actively participating in the following projects. 1) PACS: We have recently developed a radiology information system (RIS) networking with a hospital information system (HIS) and picture archiving and communicating system (PACS). The PACS of the whole hospital (the film-less imaging system) was established in 2003. The new reporting system was installed in 2012. 2) Radiation Safety Control: stimulated by the need for evaluating the individual accumulated exposure dose by medical radiation, we have started a working group to solve this problem. We aim to provide the accumulated exposure dose

data on RIS. 3) Researches on new radiology techniques: Ongoing collaborative researches are as follows: image-guided radiation therapy, clinical PET, multi-detector row CT, 3-Tesla MRI, flat panel detector, postmortem imaging, and artificial intelligence.

Clinical activities

1) Diagnostic Radiology:

The diagnostic radiology section is responsible for all the clinical examinations of CT, MRI, and angiography including interventional radiology. All of these examinations are performed under the requests of clinicians. Over two hundred CT examinations are conducted using six multi-detector-row CT scanners each day. Interventional procedures such as percutaneous biopsy and abscess drainage are also done by CT guidance. About eighty MR examinations are done using two of 1.5-Tesla and five of 3-Tesla scanners every day. Diagnostic and interventional procedures are performed using six angiographic units, including a hybrid operating room. Image Computing & Analysis Laboratory provides processing of volume image data into clinical 3D images and analysis of imaging data.

2) Nuclear medicine:

The section of nuclear medicine is responsible for all the radionuclide imaging examinations, including conventional scintigraphy such as bone, kidney, thyroid scans, single-photon emission computerized tomography (SPECT), and positron emission tomography (PET) scans. Scanning is performed on the first basement floor in the Central Clinic Building 1. Blood flow, metabolism, and receptor functions are measured to understand normal and pathophysiological states, using a variety of positron-emitter radiotracers with ^{18}F . Whole-body ^{18}F -fluorodeoxyglucose-PET (FDG-PET) for the staging of malignancy plays a vital role in the clinical management of the patients. These nuclear imaging procedures are performed and reported by radiologists and cardiologists.

3) Radiation Oncology:

The radiation therapy is performed using three linear accelerators: an intracavitary irradiation device (RALS), a brachytherapy device, and a gamma knife for radiosurgery. The network system connecting these radiotherapy pieces of equipment, CT/MR devices, and treatment planning systems was already constructed. Each year, over 700 new patients receive radiation therapy in the Radiation Oncology section. Highly accurate 3D radiation therapy is the most outstanding feature. We have developed a new linear accelerator with C-arm and multi-leaf collimator systems, mainly for non-coplanar radiation therapy in many patients, especially with brain tumors or head and neck tumors. In addition, the linear accelerator system with cone-beam CT technology has been introduced to our hospital, which enables image-guided radiation therapy.

4) Radiation safety control:

The educational training and registration of the radiation-engaging persons are controlled according to the University of Tokyo Hospital Ionizing Radiation Injury Prevention Rules.

In conclusion, the department of clinical radiology is a service section to all clinical departments. The leading supporter as a doctor is a radiologist. However, the cooperation with the radiation diagnosis and treatment engaging persons of other clinical

departments, technicians and nurses must be reinforced. We want to make still more effort to achieve the cooperation and improve clinical activities in the department of clinical radiology.

References

See the corresponding part of the Department of Radiology.

Number of examinations in 2020

	Inpatient	Outpatient	Total
Radiography (plain)	83,444	64,254	147,698
Radiography (enhanced)	3,819	1,368	5,187
Angiography	3,133	12	3,145
Computed tomography	13,763	34,744	48,507
Magnetic resonance imaging	4,633	14,813	19,446
Nuclear medicine	1,479	2,358	3,837
Radiotherapy	5,448	8,503	13,951
Bone mineral densitometry	325	2,406	2,731

Department of Pharmacy

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Introduction and Organization

We have 8 faculty members, 79 pharmacy staffs, and 8 graduate students and 8 undergraduate students from the faculty of pharmaceutical sciences (as of March 1st, 2021).

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 (2,654 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 2020)

Number of items on in-hospital formulary: 2,654

Number of prescriptions (ps.) filled or preparation (pp.) (annual)

out-patients	:	320,766 ps.
(outside	:	287,512 ps.)
(inside	:	33,254 ps.)
out-patient chemotherapy:		11,983 ps.

in-patients : 231,367 ps.

injection drugs : 184,428 ps.

IVH : 3,213 pp.

chemotherapy : 10,225 pp.

TDM consultations (annual) : 18,973 pp.

Numbers of hospital pharmaceutical cares (annual):
20,234 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 pharmaceuticals 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 2017, 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 2020, 11 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.

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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 moxibustion. In the Day-care Unit, clinical psychologists and nurses also work. In 2006, speech therapists who had belonged to other departments in the University of Tokyo Hospital were included in our department. From 2009, a speech therapist added to our department, and now three therapists perform therapy for patients with aphasia, dysarthria, and dysphagia.

Clinical activities

The professor serves as a director of Rehabilitation Center, the University of Tokyo Hospital. The Rehabilitation Center and the Department of Rehabilitation Medicine are united and engage in clinical practice. We have at present no charged ward, and treat about 4,700 new referrals annually from almost all the departments of the university hospital. We always take charge of 250-300 patients corresponding about 25-30% of the whole number of inpatients. We also see 15 people per day at the outpatient rehabilitation setting. The numerical ratio of outpatient is being reduced in order to give priority to the clinical service

corresponding to needs expansion of service to inpatients.

Teaching activities

We have provided several clinical curriculums on rehabilitation medicine for 4th, 5th, and 6th year medical students since 1973. The systematic lecture series for 4th year medical students (M2) include the subjects on rehabilitation for disorders such as cerebrovascular disturbances, respiratory disorders, neuromuscular diseases, bone and joint diseases, and pediatric disorders as well as on outline of rehabilitation, and amputation/prostheses. We have provided a clinical practice in small group, so-called clinical clerkship for 5th and 6th year students from Wednesday to Friday every week. They experience a few patients and learn how to take a patients' history, physical findings, functional evaluation, and how to plan rehabilitation programs. We have introduced a few of elective students for elective clinical clerkship to our collaborating hospitals with specialized rehabilitation ward.

In addition, we have provided the training of students including physical therapy, occupational therapy, and speech therapy. Twenty students or more come and stay at the university hospital annually as a long-term clerkship from several PT/OT/ST training schools.

Research activities

Our research activities are growing up. In 2006, the Rehabilitation Center moved to the new building and a research laboratory was provided for the first time. As the motion analysis system was partially renewed, we are planning our researches mainly in the field of musculoskeletal disabilities. In addition, we are planning collaborating researches with other departments in our hospital, other faculties in our university, and institutions outside the University of Tokyo. The ongoing and scheduled projects are as follows.

- 1) 3D Motion analysis of patients with musculoskeletal disorders
- 2) Study on the relationship between sensory deficit and motor control
- 3) Rehabilitation and long-term outcome in patients with skeletal dysplasias

- 4) Pathology and treatment for patients with congenital limb deficiencies
- 5) Analysis of rehabilitation outcome using DPC data

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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, 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

Division of Diagnostic Pathology

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Deputy Director

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

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

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Project Professor

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Introduction and Organization

Department of Pathology and Diagnostic Pathology and Division of Diagnostic 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 Geneprofileing 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 2020 fiscal year consisted of 15,450 surgical cases, 14,154 cytology, 933 intraoperative histologic diagnosis, 371 intraoperative cytology, 44 autopsy cases (autopsy rate, 15.4%). Limited hospital activity due to COVID-19 pandemic resulted in the decrease of the number of specimens.

The following surgical pathology conferences are regularly held; thoracic organs (Drs. Shinozaki-Ushiku 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 Makise), kidney (Drs. Abe and Hinata), and skin (Dr. Tanaka).

We provide FFPE specimens suitable for multiplex genomic testing. We also join clinicopathologic and genomic conference which is held every week to present histology of the cases and join the discussion.

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 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 Division of Diagnostic Pathology accepted six junior residents (total 12 months) in 2020 for their second-year program.

Research activities

We are working on the pathologic research projects of neoplastic diseases based on observation obtained from pathologic diagnosis as well as discussion with clinicians at surgical pathology conferences.

To develop AI-based pathology diagnosis system, some projects are currently in progress. Dr. Abe focuses on gastrointestinal tract biopsy diagnosis using machine learning. Dr. Hinata has developed an automatic system to detect immunotherapy-sensitive subtype in gastric cancer using histologic image-based deep learning.

The development of automatic grossing and sectioning system using AI-equipped robot is also in progress as collaborative research with engineering faculty-of the University of Tokyo (Prof. Mamoru Mitsuishi).

We continue the study to investigate the usefulness of post-mortem CT images for hospital autopsy in collaboration with the department of radiology. We obtain post-mortem images with a CT apparatus in the autopsy-assisting CT room and compare the results with those of autopsy to better understand the patients' pathophysiology.

In addition, a lot of collaborative research projects are also being conducted with various departments and laboratories.

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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). Contact lens clinic for keratoconus and post-keratoplasty eyes and keratoconus clinic for providing corneal crosslinking surgery, which is a brand-new treatment to halt keratoconus progression, were held in the afternoon of Thursday. At the corneal service, we determine indication for corneal transplantation and follow up patients after the surgery. Total 61 corneal surgeries including keratoplasty were

performed in 2020. In addition to the full-thickness corneal transplantation (penetrating keratoplasty), we have successfully performed corneal endothelial transplantation for patients with bullous keratopathy, the most common disease of corneal transplantation. Generally, corneal transplantation is performed as emergency operation, because we need to transplant corneas as soon as possible.

The other important activities of the section include mediation of donor eyes to other university hospitals and medical institutes that need donor eyes for corneal transplantation with cooperation of Eyebank. We are also performing corneal transplantation using corneas from American Eyebank as needed.

Followings are our main clinical themes to be pursued to improve the safety and prognosis of corneal transplantation.

- 1) Positive proof that donors were free of such infectious diseases as viral hepatitis, syphilis, AIDS and acute T-cell leukemia to prevent transmission to recipient patients through grafting.
- 2) Postoperative clinical outcomes are evaluated in regenerative medicine for ocular surface reconstruction, such as cultured corneal limbal, oral mucosal and conjunctival epithelial sheet transplantation on the amniotic membrane, full-thickness corneal transplantation, lamellar keratoplasty, and endothelial keratoplasty.
- 3) Critical factors to affect clinical outcomes are statistically investigated in various kinds of

corneal operation technique.

Teaching activities

We give lectures on corneal diseases and corneal transplantation to medical students and practitioners. In addition, we are engaged in practical training for young ophthalmologists on ophthalmological examinations at the outpatient clinic.

Research activities

We are conducting clinical research of post-operative results of DSAEK, clinical results of corneal crosslinking, and clinical research of corneal biometry by using anterior segment OCT.

In addition, we are investigating the delivery of nucleic acid based drug in corneal neovascularization or corneal dystrophy, genetic analysis and genome editing for corneal dystrophy.

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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 2020, 25 patients (including 1 children) received autologous HSCT and 39 patients (including 8 children) allogeneic HSCT. We cooperate with the members of Department of Hematology and Oncology, Hematology/Oncology group in the Department of Pediatrics, and Department of Transfusion Medicine.

Allogeneic hematopoietic stem cell transplantation:

Bone marrow cells are operatively harvested and infused without preservation. For peripheral blood stem cell transplantation, leukapheresis is performed with the use of an automated continuous flow blood cell separator, and harvested cells are preserved at -196°C in cooperation with Department of Transfusion Medicine. Recently, transplantation after pre-conditioning of reduced intensity (RIST for reduced-intensity HSCT or NST for non-myeloablative HSCT) is commonly performed for the elderly and patients with organ dysfunction. The development of this strategy is expanding the eligibility of transplant recipients.

Some patients cannot get transplantation treatment because they don't have eligible donors with at least a 90% match of HLA. Recently, with the development of new methods of transplantation management, such as immunosuppression, it has become possible to safely carry out transplants from donors with a 50% HLA match (HLA haploidentical transplantation; haplo transplants), and the procedure is expected to spread more widely in the future. The department proactively performs haplo transplants for patients in need to overcome diseases.

Allogeneic HSCT for the elderly and HLA haploidentical transplantation are performed under the admission of Patient Relations and Clinical Ethics Center.

High-dose chemotherapy with or without autologous stem cell support: High-dose chemotherapy is administered according to the malignant disease. For the autologous stem cell support, peripheral blood stem cell is usually selected as a source of stem cells. Similar procedures used in the allogeneic stem cell harvest are performed for leukapheresis and preservation of autologous stem cell.

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.

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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 gastrointestinal endoscopy, colonoscopy, bronchoscopy, otorhinolaryngological endoscopy and gynecological endoscopy, are performed from Monday to Friday. Emergency endoscopy is performed in the nighttime or holidays. The numbers of endoscopic procedures in each field are increasing gradually year by year and the total number during 2016 reached to 20,000. In the gastrointestinal tract, image enhanced endoscopy for detailed inspection and therapeutic endoscopy, including endoscopic submucosal dissection for esophageal, gastric and colorectal tumors, are major advanced fields. In addition, endoscopic diagnosis and management of pancreatobiliary diseases is also performed. Our recent clinical activities are

summarized in Table 1.

Another important activity of our department is the disinfection and maintenance of endoscopic apparatuses used in other units including the outpatient clinic, radiotherapy department, surgery department or intensive care units. Endoscopes in our hospital are collected in our department after use and disinfected.

In 2020, 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.

Table 1. Endoscopic examinations in the Department of Endoscopy and Endoscopic Surgery

	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
EGD*	10963	11376	11840	11740	11874	11944	11490	11699 (2177)	11226 (2501)	8,906
Colonoscopy	5208	5688	6000	6043	6394	6814	5921	5530 (109)	5675 (329)	4,548
Bronchoscopy	197	196	169	218	228	362	350	316	395	300
ERCP**	1072	956	912	1035	946	1206	1137	1057	1314	1302
EUS†	630	698	763	766	882	1084	1023	923	1059	711
Enteroscopy	282	282	375	396	310	86	304	138	151	74
Laryngoscopy	108	83	128	102	105	125	114	92	102	42
Colposcopy	378	365	404	327	295	417	430	414	392	333
Total	18838	19644	20591	20627	21034	22038	20769	20169	20314	16226

*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.

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Department of Hemodialysis and Apheresis

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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 inflammatory bowel diseases such as ulcerative colitis.
7. Cell-free and concentrated ascites reinfusion therapy (CART) for refractory ascites.
8. Induction and maintenance of peritoneal dialysis for 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].

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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/u hosp/>

- 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.

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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 Quality & 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 Quality & Compliance are as follows: (1) auditing of clinical researches and clinical trials, (2) giving guidance and advice on the reliability of clinical trials, (3) performing trend-analysis of audit findings and compliance issues, report and make recommendations to the hospital director to become a high reliability organization, (4) providing support for the preparation of GCP inspections by regulatory

authorities, and integrated management of findings, (5) integrated management of outsourced auditing, (6) integrated management of audit results of the University of Tokyo Hospital, (7) collecting information for corrective action and preventive action after audits and investigations, (8) collecting and analyzing regulatory information on reliability of clinical research/trials, and providing education/training, and (9) the secretariat of the Auditing Working Group of Core Centers' Network for Translational and Clinical Research, Project of Translational and Clinical Research Core Centers, TR-SPRINT (AMED).

The Department of Clinical Research Governance consists of a director (full-time post from August, 2015), a Research Associate/URA in the Office of Strategic Planning and Promotion, and 7 staffs (4 auditors and 3 temporary staffs (auditor/audit-assistant/support staff)) in the Office of Clinical Quality & Compliance as of March 2019. The Office of Research Integrity and Promotion. has no additional member, and the director serves as it.

Activities

The Office of Strategic Planning and Promotion has undertaken the following activities in fiscal year 2018.

- 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, Labour and Welfare.
- 2) Others: investigations of research paper publication activities, co-operating the "Forum for Development of Seeds for Advanced Medicine", etc.

The Office of Clinical Quality Assurance & Compliance has undertaken the following activities in fiscal year 2018.

- 1) Audit activities: (1) As regards to trials/researches conducted by the University of Tokyo Hospital, the office conducted 4 audits for investigator-initiated

clinical trials, 3 audits for Specified Clinical Researches, and 2 audits for other trials. (2) One audit for investigator-initiated clinical trial conducted at other university hospital which lead by the University of Tokyo Hospital. (3) One audit for investigator-initiated clinical trial conducted at other university hospital. (4) provided assistance in the preparation of audit SOPs and audit plan, etc. for other some clinical trials and researches.

2) Support for surveys/investigations: Regarding TR Core Centers surveys by AMED, and Clinical Research Core Hospital investigations, the Office attended to explain the system and structure of quality assurance, etc.

3) 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.

4) Advisory: provided advice on compliance and reliability related matters to the Central Coordinating Unit, Site Coordinating unit, and prepares advisory records.

5) TR program: In June/2017, the University of Tokyo Hospital was appointed as the secretariat of new initiative, Audit Working Group of AMED described above. The Working Group consists of one to three auditors from each Center. The secretariat conducted three meetings with all members (May 5th, November 6th, and March 12th), one Training for auditors (March 5th), and 24 times meetings in total on three themes (1) Auditors education and training, (2) Collect issues in auditing and solve them, and (3) Optimal conduct of audit & quality assurance, at each sub-working group.

6) Networking: (1) As a part of UCHT Alliance activity, monitoring took place among the eight member universities in the Kanto Koshinetsu region to evaluate the implementation system. (2) Participated in the study to evaluate the reliability as a part of the National University Hospital Clinical Research Promotion Initiative (NUH-CRPI). (3) Participated in the Japan Society of Quality Assurance (JSQA).

Department of Child Psychiatry

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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 2020, 7 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 2020 was 173, which was about two-thirds of the number of new patients last year. This decrease seemed to be affected by the restriction on outpatient care due to the spread of COVID-19 infection. More than 70% of the new patients consisted of patients with ASD, ADHD or tic disorders. Out of 173 patients, children of elementary school age were 64, and children of junior high school age were 34. In other words, children of elementary or junior high school age were more than half of the patients. Number of preschool children was 62, 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. 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.

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 internet 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.

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Tissue Bank

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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 supply since 2018. Dissemination and educational activities for the advancement of tissue transplantation and transplantation medicine is our important mission. In this line of effort, starting 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 six Clinical Divisions (Gastroenterology, Breast and Endocrine Surgery, Gynecologic Surgery, Ophthalmology and Vision Collection, Neurology, and Geriatric Medicine).

The staff of the Center for Epidemiology and Preventive Medicine is composed of ten physicians (eight regular physicians and one physician from the related departments). Three of the regular physicians also perform upper gastrointestinal endoscopy and colonoscopy. Our department also has nine nurses, five assistant clerks, and one medical clerk.

Clinical activities

In addition to basic examinations, we provide nine 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, and 9) estimation of gastric cancer risk. While meeting the needs of examinees, we have increased the number of the optional examinations. We have provided pancreatic cancer screening from September 2020.

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

In the fiscal year (FY) 2020 (from April 1, 2020 to March 31, 2021), our center was suspended from April 20 to May 31, 2020 due to coronavirus. Respiratory function test has been cancelled from March 31, 2020 and gastrointestinal endoscopy has been cancelled from April 9 to June 8, 2020.

The total number of examinees (who had basic examinations and optional examinations) in the FY 2020 was 6963 including 2557 in basic examinations, 431 in complete cardiovascular examinations, 542 in complete cerebrovascular examinations, 57 in check up for dementia, 287 in colorectal cancer screening, 524 in uterine cancer screening, 665 in breast cancer screening, 564 in lung cancer screening, 1028 in tumor marker diagnosis, 203 in estimation of gastric cancer risk, and 17 in upper gastrointestinal endoscopy (later). Although check up for dementia was discontinued in December 2018, we restarted this examination in June 2020.

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 2020, we issued 1192 letters of referral to other departments in our hospital and 36 to other hospitals.

We have expanded our public relations efforts and 15,000 brochures were delivered during the FY 2020.

We also prepared posters which were placed within our hospital and on the campus of the University of Tokyo as well. We have established our original website (<https://www.todai-yobouigaku.com/>) 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.

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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

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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. Also, we are cooperating holding and teaching MCLS, Mass Casualty Life Support, courses of Japan Association for Disaster Medicine, and JATEC, Japan Advanced Trauma Evaluation and Care, courses of Japanese Association for Acute Medicine, and so on.

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.

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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.

Department of Clinical Nutrition Therapy

Head of the Center

Kazuhiko Fukatsu (Professor)

Assistant Head of the Center

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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 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 Exhibit has been conducted every year for over 20 years.

In 2001, integration of the branch hospital with the main hospital resulted in an 8-manual- 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.

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., mothers' classes, etc.

In 2020, due to the COVID-19 pandemic situation, the instances of nutritional guidance of inpatients and outpatients decreased, but recovered in the last half of the year and resulted in 2686 instances for inpatients and 4865 instances for outpatients. Nutritional guidance for malignant tumor patients was performed for 424 instances. Perioperative guidance was 70 instances.

In July 2012, a physician, managerial dietitian, and nurse formed a dialysis prevention team, and started calculating fees for diabetes and dialysis prevention guidance and management in the outpatient clinic. The managerial dietitian and nurse provide guidance on Wednesday and Thursday afternoons, and there were 145 guidance sessions in 2020.

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. In 2020, due to the COVID-19 pandemic, only 84 instances were calculated, because the round was performed by fewer team members for reduced number of patients without calculating the NST charges for several months.

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.)

In 2017, the department was involved in the curriculum of Clinical Clerkship, the medical education program of the Faculty of Medicine, the University of Tokyo. 116 medical students at M4 grade participated in the two-day practice course in 2020.

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 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”
- Joint research with the Department of Hepatobiliary and Pancreatic Surgery
Research topic: “Assessment of perioperative improvement in nutrition status by an open trial of branched amino acids formula in patients of hepatocellular carcinoma derived from liver cirrhosis with abnormal ICG_{R15} and patients who have undergone liver transplantation”

Research topic: “Feasibility study assessing improvement of postoperative complication rate by introducing home enteral feeding for patients who have undergone pancreaticoduodenectomy”

- Joint research with multiple institutes directed by Chiba University

Research topic: “Interventional study to discover the appropriate target body weight for effective treatment strategy and improvement of health disorder of obesity patients”

- Joint research with the Department of Stomach and Esophageal Surgery

Research topics: “A randomized control trial evaluating exercise and nutritional intervention for gastric cancer patients in the perioperative period for sarcopenia prevention”

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Department of Clinical Genomics

Director & Professor

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

Associate Professor

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

Organization

The Department of Clinical Genomics started as a special unit providing clinical genomics services in 2003. The department functions as the core unit to provide genetic counseling services to support an appropriate and efficient application of genetic testing, as well as genomic medicine in cancer. The department also provides a training program for physicians preparing for board-certified clinical geneticists. Many medical staffs with diverse specialties including pediatricians, obstetricians, neurologists, cardiologists, diabetologists and surgeons participate in the activities of the Department.

Activities

Genetic Counseling

The room (Room 200) is specifically allocated in the outpatient clinic. Genetic counseling is performed by a team of board-certified clinical geneticist and certified genetic counselors in cooperation with other clinical departments. All cases are reviewed and discussed at the conference which is held once every month. We also provide support to clinical departments for establishing genetic diagnosis in various types of diseases, including neurological disorder, pediatric and perinatal disorders, Marfan's Syndrome and Hereditary Breast and Ovarian Cancer.

Genomic Medicine in Cancer

We provide cancer genomic profiling (clinical sequencing) for incurable malignant solid tumors with 12 collaborative hospitals, as a "Cancer Genome Core Hospital". Two types of cancer genomic profiling

(OncoGuide™ NCC Oncopanel System, FoundationOne® CDx Cancer Genomic Profiling) were approved by PMDA in June, 2019. FoundationOne® Liquid CDx Cancer Genomic Profiling 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).

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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. It belongs to the central clinical division 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-sponsored 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-initiated medical treatment 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.

<Sponsor-Initiated Clinical Trials Promotion Department>

The department is responsible for: (1) Supporting the safe and smooth implementation of sponsor-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 New 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-sponsored 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 Support 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 (23 papers in English and 7 papers in Japanese).

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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 m² laboratory on the 8th floor of the In-patient Ward B. In May 2016, it moved to Molecular and Life Innovation building. Division of Tissue Engineering consists of Department of Bone & Cartilage Regenerative Medicine, Department of Cell & Tissue Engineering (until 31 Oct, 2020), and Laboratory for Pediatric Regenerative Medicine. One project associate professor and one project research associates who are assigned to each department are conducting research with many graduate students. The researchers continue their studies to make the center function as a translational research center.

Tie-up with companies, technical transfer, patenting developed technologies, producing materials for treatment at a GMP level, safety evaluation studies and organization for clinical trials are necessary in order to realize regenerative medicine, which is now recognized

as a national project. As foundation and operation of venture companies as well as industry-university-government cooperation is essential to the success, it seems that state-level efforts are necessary. It is expected that broad progress in tissue engineering technologies and regenerative medicine contributes to treatment and drug discovery of all medical fields regardless of specialties.

October, 2001 Division of Tissue Engineering founded as a special medical office in the University of Tokyo Hospital.

June, 2002 Department of Corneal Tissue Engineering founded by a donation from HOYA health care CO., Ltd.

July, 2002 Department of Vascular Regeneration founded by a donation from Daiichi Pharmaceutical Co., Ltd.

July, 2002 Department of Bone & Cartilage Regenerative Medicine founded by a donation from TAKEDA Chemical Industries., Ltd.

September, 2002 Department of Regeneration

Medicine for Hematopoiesis founded by a donation from KIRIN Brewery Co., Ltd.

November, 2002 Department of Clinical Renal Regeneration founded by a donation from MOCHIDA Pharmaceutical Co., Ltd.

November, 2002 Department of MENICON Cartilage & Bone Regeneration founded by a donation from MENICON Co., Ltd.

March, 2003 The Cell Processing Center set up on the 8th floor of the In-patient Ward B.

June, 2005 Department of Corneal Tissue Regeneration was renewed by a donation from AMNIO TEC Co., Ltd.

July, 2005 Department of Bone & Cartilage Regenerative Medicine was renewed by a donation from TAKEDA Chemical Industries Co., Ltd.

September, 2005 Department of Regeneration Medicine for Hematopoiesis was renewed by a donation from KIRIN Brewery Co., Ltd.

November, 2005 Department of Clinical Renal Regeneration was renewed by a donation from MOCHIDA Pharmaceutical Co., Ltd.

November, 2005 By a donation from FUJISOFT ABC Co., Ltd. Department of MENICON Cartilage & Bone Regeneration was renewed to Department of Fuji Software ABC Cartilage & Bone Regeneration.

January, 2007 Laboratory for Pediatric Regenerative Medicine was founded by department of pediatric surgery.

July, 2007 Department of Bone & Cartilage Regenerative Medicine was renewed by a donation from Eli Lilly Japan K.K.

March, 2012 Department of Advanced Nephrology and Regenerative Medicine founded by a donation from Zenjinkai.

April, 2016 The Cell Processing & Banking Center set up on the 4th floor of the Molecular & Life Innovation Building.

November 2017 Change of the department name: Department of Cartilage & Bone Regeneration became Department of Cell & Tissue Engineering.

July, 2018 Department of Bone & Cartilage Regenerative Medicine was renewed by a donation from Avenue Cell Clinic, Kaneka Corporation, Rohto Pharmaceutical Co., Ltd. and Nichirei Corporation.

November, 2019 Department of Tissue Stem cell/Life Dentistry established by Dental assist Co., Ltd,

Fuke hospital, Sashiogi Hospital, Ikegami Home Clinic and Inotec Co., Ltd.

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 the Department of Cell & Tissue Engineering, we aimed 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. To achieve these goals, we conducted research on adult stem cell biology in mesenchymal tissues, application of molecular biology on cartilage repair for regenerative medicine, 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. Based on the findings and knowledge gained through this clinical study, another investigator-initiated clinical trial applying implant-type tissue-engineered cartilage for the treatment of tracheal stenosis has also been approved. 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.

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【Book】

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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 Cooperative Unit of Medicine and Engineering Research

was organized by representative members of relevant clinical departments. The committee made a decision of the following basic principles; recruitment for the participation to this unit should be, as a general rule, an open call for a joint project of clinical department and engineering or pharmaceutical research group in The University of Tokyo, an equipment/administration expense of a laboratory should be a responsibility of the user, and a basic participation period to this unit should be three years and for the continued participation in the unit, a review and approve of the steering committee is indispensable.

2002 October. An open call for participants to this unit started. There were 18 applications and the steering committee approved all projects after review. A liaison conference of Cooperative Unit of Medicine and Engineering Research was organized by a representative member of each project. Configuration

of each project in a space of 554.4m² that is consisted of a portion of the first floor and the basement of an administration building came to a decision by the conference.

2003 May. The construction of Cooperative Unit of Medicine and Engineering Research was completed. The cost of the construction was shared by the participation groups.

2003 May 22. The first research meeting of Cooperative Unit of Medicine and Engineering Research took place and research activities started.

2004 September 3. The second research meeting of Cooperative Unit of Medicine and Engineering Research took place.

2005 September 13. The third research meeting of Cooperative Unit of Medicine and Engineering Research took place.

2006 December 21. The fourth research meeting of Cooperative Unit of Medicine and Engineering Research took place.

2007 December 13. The fifth research meeting of Cooperative Unit of Medicine and Engineering Research took place.

2009 December 3. The sixth research meeting of Cooperative Unit of Medicine and Engineering Research took place.

2011 February 2. The seventh research meeting of Cooperative Unit of Medicine and Engineering Research took place.

2011 December 17. The eighth research meeting of Cooperative Unit of Medicine and Engineering Research took place.

2013 January 25. Development forum of advanced medical seeds took place

2014 January 24. Development forum of advanced medical seeds took place

2015 January 22. Development forum of advanced medical seeds took place

2016 February 2. Development forum of advanced medical seeds took place

2017 February 2. Development forum of advanced medical seeds took place

2018 February 1. Development forum of advanced medical seeds took place

2018 October. Each lab was moved from the the first floor and the basement of an administration building, based on the decision of redistribution of

hospital facility

2019 February 18. Development forum of advanced medical seeds took place

2020 January 21. Development forum of advanced medical seeds took place

2021 February 10. Development forum of advanced medical seeds took place

Research activities

Development of Advanced Stereotactic Radiation Cancer Therapy System

Department of Radiology

Nuclear Professional School, Department of Nuclear Engineering and Management

Department of Chemical System Engineering

High Precision Stereotactic X-ray Cancer Therapy System. Development of Advanced Compact Electron Linear Accelerator for Cancer Inspection and Therapy The aim of this research is to apply the in-vivo visualization technique developed by our group in high-precision radiation therapy and to develop the motion prediction system for a real-time tumor-tracking radiation therapy. For the visualization of the treatment area during treatment, a four-dimensional cone-beam computed tomography (4D CBCT) reconstruction algorithm is developed by taking the anatomy or tumor motion analysis into account. In-treatment 4D CBCT requires the projection images acquired during treatment. The projection images are analyzed online, and compared with the reprojection images from the treatment planning CT or registration CT. The time lag due to the analysis can be compensated by the prediction using a multi-channel singular spectrum analysis. This system will remove a delay problem during the real-time tumor-tracking radiation therapy, and will provide a safer radiation therapy than the current ones because this will be able to detect an irregular breathing motion of the tumor.

Research and development of micro-neurosurgical robotic systems

Department of Neurosurgery, The University of Tokyo Hospital

Mitsubishi Laboratory, Department of Mechanical Engineering, School of Engineering

Development of micro-neurosurgical robotic systems and advanced microscopic image processing for autonomous surgical task recognition.

Development of Support Systems for Risk Reduction in the Clinical Process

Chemical System Engineering

Center for Epidemiology and Preventive Medicine

Our specific targets are research and education on the integration of biological and clinical information including genome. In particular, we focus on establishment of personalized medicine as translational research, selection of drug targets by proteomics, interpretation of transcriptional regulations and drug development by targeting transcriptional factors in metabolic and cardiovascular diseases. Also, analyses of genomic functions, clinical safety monitoring by clinical database and assessments of clinical information systems are conducted.

Project of Neutron Capture Therapy & Innovation of DDS for Cancer

Department of Cardiothoracic Surgery, Graduate School of Medicine

Institute of Engineering Innovation, School of Engineering

Department of Bioengineering, School of Engineering

In order to control and eliminate human cancers, we develop the neutron capture therapy (NCT) using small neutron accelerator equipped to hospital and also aim to augment cancer therapy combined with approaches of Drug Delivery System. We develop the tumour specific drug delivery systems entrapped boron or gadolinium compounds as neutron capture agents (WOW emulsion, Nano-micelle, Cationic Polyplex).

Development of adhesion barrier materials using a new animal model of liver-peritoneal adhesion

Artificial Organ and Transplantation Division, Department of Surgery, Graduate School of Medicine, University of Tokyo

Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, University of Tokyo

Organs and Biosystems Engineering Laboratory,

*Institute of Industrial Science, The University of Tokyo
Division of Biomedical Equipment and Biomaterials,
Center for Disease Biology and Integrative Medicine,
Graduate School of Medicine, The University of Tokyo
Department of Chemical System Engineering,
Graduate School of Engineering, The University of Tokyo*

Department of Bioengineering, Graduate School of Engineering, The University of Tokyo

Adhesions between liver and other organs are an important issue in the cases of second surgeries such as hepatic resection. Adhesions extend operative duration; in addition, they increase the risk of surgeries. Thus, it is important to avoid adhesions at a first surgery. However, no one report both the animal model and adhesion barrier materials of liver adhesion. We try to develop a new adhesion model by hepatic resection, instead of a usual peritoneal abrasion model. Also, we develop new materials for preventing the adhesions.

Development of new therapy of life style-related diseases by Applied Metabolic Biotechnology

Department of Cardiovascular Medicine, Graduate School of Medicine

Department of Diabetes and Metabolic Diseases, Graduate School of Medicine

Department of Chemistry and Biotechnology, School of Engineering

To establish the system and methods for engineering the novel model mice of life style-related diseases using RNAi technology and biotechnology. To elucidate the mechanisms by which adipose tissue derived factors, adipokines, contribute to the development of the metabolic syndrome. To explore the molecular mechanisms of sarcopenia.

Development of bone and cartilage regeneration by scaffold and mechanical stress

Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo

*Division of Science for Joint Reconstruction, Graduate School of Medicine, The University of Tokyo
Ishihara & Takai Lab, Department of Materials Science, Graduate School of Engineering, The University of Tokyo*

Laboratory of Regenerative Medical Engineering,

*Center for Disease Biology and Integrative Medicine,
Faculty of Medicine, The University of Tokyo*

*Department of Oral and Maxillofacial Surgery,
Faculty of Medicine, The University of Tokyo*

Inhibition of aseptic loosening of artificial joints by nano-grafting of a novel biocompatible polymer MPC. Creation of biocompatible biomaterials optimized for bone, cartilage and vascular regeneration. Regeneration of bone and cartilage tissue in vitro promoted by physical stimulation

Development of a non-viral gene delivery system by supramolecular nanotechnology.

Department of Materials Science, Graduate School of Engineering, The University of Tokyo

Department of Bone & Cartilage Regenerative Medicine, Graduate School of Medicine, The University of Tokyo

Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo

Department of Oral and Maxillofacial Surgery, Faculty of Medicine, The University of Tokyo

Division of Clinical Biotechnology, Center for Disease Biology and Integrative

Medicine, Graduate School of Medicine, The University of Tokyo

Division of Tissue Engineering, The University of Tokyo Hospital

Development of a non-viral siRNA delivery system by supramolecular nanotechnology. Production of regenerated cartilage and bone with high safety and usefulness. Establishment of practical production and quality control systems. Promotion of the clinical application of regenerated cartilage and bone. Development of easy, precise, non-invasive systems to detect osteoblastic and chondrogenic differentiation. Determination of a finite set of signaling factors sufficient for induction of osteoblasts and chondrocytes. Development of a method to induce osteogenesis and angiogenesis simultaneously. Development of a cell-sheet culture system for bone and cartilage. Screening for compounds that induce bone and cartilage regeneration

Development of gene therapy of cardiovascular therapy by polymeric micelles.

Department of Vascular Surgery, Division of Tissue Engineering, The University of Tokyo Hospital

Kataoka Laboratory, Department of Materials Science and Engineering, Graduate School of Engineering, The University of Tokyo

To achieve effective and safe in vivo gene therapy of cardiovascular and vascular diseases, we are developing non-viral gene vectors based on nano-scaled polymer assemblies (polymeric micelles). Polymeric micelles, which are spontaneously formed from block copolymers, have a core containing packaged genes surrounded by biocompatible poly (ethylene glycol) (PEG) palisades, and a variety of pilot molecules can be installed on the surface of polymeric micelles. This "virus-mimicking" nanoparticles might achieve efficient gene transfer to the targeted tissues or cells because of protection of the loaded DNA from nuclease attack, their lowered non-specific interaction with proteins and cells and facilitated internalization by the targeted cells through specific interaction of the pilot molecules. Currently, our research has been focused on in vivo gene transfer to artery walls and muscles using polymeric micelles incorporated genes.

Development and application of biomolecule visualization probes

Department of Cardiovascular Medicine

Laboratory of Chemistry and Biology, Graduate School of Pharmaceutical Sciences

We have developed biomolecule visualization probes and investigated model animals for application. As a biomolecule visualization probe, we are improving and more applying fluorescent probes for cancer lesion detection. Moreover, we are going to develop labeled probes which can elucidate disease treatment mechanism of microRNA and adipose stem cells. Now as fundamental study, we are researching disease models for applying these treatments. In particular, we are investigating diabetic nephropathy, liver fibrosis and atherosclerosis models as non-coding RNA and adipose stem cells treatment targets.

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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 Project 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, renal dysfunction, and atherosclerosis obliterance (ASO) in the Japanese population. We are now performing a genome-wide association study to identify variations conferring susceptibility to type 2 diabetes in the Japanese population. About 500,000 variants directly genotyped were imputed using the 1000 Genomes Project Phase 3 reference panel in 36,000 cases and

more than 155,000 controls. We identified novel type 2 diabetes associated loci, which had distinct minor allele frequency spectra between Japanese and Europeans, such as the missense variants in genes related to insulin secretion. Trans-ethnic comparisons of the molecular pathways from the genome-wide association study (GWAS) results highlighted both ethnically shared and distinct impacts of a series of pathways on type 2 diabetes. These findings illustrated the etiology of type 2 diabetes in Japanese and Europeans. We identified 88 type 2 diabetes-associated loci, of which 28 loci were novel. Twenty-eight missense variants were in linkage disequilibrium with the lead variants, including missense variants in genes related to insulin secretion (GLP1R) (Suzuki K, et al. Nat Genetics 51, 379-386, 2019). Mahajan et al. reported type 2 diabetes genome-wide association study meta-analysis data on approximately 900,000 individuals of European ancestry, increasing the association signals in over 240 loci associated with type 2 diabetes (Mahajan A, et al. Nature Genetics 50, 1505-1513, 2018). Type 2 diabetes GWAS meta-analysis performed in a Japanese population identified no less than 20 novel type 2 diabetes loci that were not associated with type 2 diabetes in Europeans. This article is referenced in the position statement from science council of Japan.

To examine type 2 diabetes risk in East Asian individuals, our team carried out a meta-analysis of GWAS data from 77,418 individuals with type 2 diabetes and 356,122 healthy control individuals. We identified 61 loci that are newly implicated in predisposition to type 2 diabetes. (Spracklen CN, et al. Identification of type 2 diabetes loci in 433,540 East

Asian individuals, *Nature* 582, 240-245, 2020).

We conducted whole genome sequence and analyzed the sequence data of 1,987 subjects with type 2 diabetes in collaboration with the Osaka University, RIKEN and BioBank Japan. We conducted metabolome analysis and analyzed the data of 300 subjects with diabetic complications. 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 are interviewed and contributed to the report by the project of Japan Agency for Medical Research and Development (AMED) concerning ethical, legal and social issue of secondary findings in genomic research (Aizawa Y, et al. A proposal on the first Japanese practical guidance for the return of individual genomic results in research settings. *J Hum Genet.* 65, 251-261, 2020).

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.

new susceptibility loci for type 2 diabetes in the Japanese population. *Nat Genet.* 2019 Mar; 51(3): 379-386. doi:10.1038/s41588-018-0332-4. Epub 2019 Feb 4.

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Immune-Mediated Diseases Therapy Center

Professor

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Lecturer

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Homepage <http://www.m.u-tokyo.ac.jp/patients/depts./menekishikkan/>

Introduction and Organization

Since the introduction of TNF inhibitors for rheumatoid arthritis in Japan in 2003, biologic agents targeting cytokines and selective small-molecule inhibitors of intracellular signal transduction events have been developed and have shown significant results in the treatment of various immune-mediated diseases. These drugs are called “molecular targeted therapies” and are targeted at diseases such as rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, Behcet's disease, autoinflammatory diseases, spondyloarthritis, psoriasis and psoriatic arthritis, inflammatory bowel disease, multiple sclerosis, nocturnal paroxysmal hemoglobinuria, and recently expanded to atopic dermatitis. Currently available molecular targeted agents are 8 TNF inhibitors, 3 IL-6 inhibitors, 1 CTLA4-Ig, 3 IL-17 inhibitors, 1 IL-12/23 inhibitor, 2 IL-23 inhibitors, 2 α 4 integrin inhibitors, 2 IL-5 inhibitors, 1 IL-4/13 inhibitor, 1 anti-IgE antibody, 1 IL-1 inhibitor, and 5 JAK inhibitors. Molecular targeted agents are not only highly effective, but are also expected to reduce the long-term side effects of steroids by reducing the dosage of corticosteroids, which are often used for immunological diseases.

In 2017, with the expansion of molecular targeted

agents, the “Immune-mediated Diseases Therapy Center Outpatient Department” was established in the outpatient consultation division. In order to further increase the number of molecular targeted agents and expand the range of indications, it was approved as a department of the University of Tokyo Graduate School of Medicine in April of last year (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. We also hold a bimonthly meeting of the Immune Disease Treatment Center as a place to share information and improve problems.

The current number of prescriptions for molecularly targeted agents has more than doubled from 550 in 2017 to 1,300 in 2020, 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.

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Medical Community Network and Discharge Planning Center

Associate Professor

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Assistant Professor

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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 medical treatment: The Department provides assistance to outpatients referred from local medical institutions. Our staff helps patients make appointments and follow procedures to receive medical treatment. The Department assists new outpatients in arranging general consultations, helps outpatients schedule specialized treatment, and provides assistance to patients who have been referred to a specific physician.

Assistance to inpatients upon discharge: The

Department provides assistance to patients for whom transfer to a local medical institution or discharge to home if need arises.

Many of such patients are highly dependent on medical care due to the severity of their condition. For those receiving medical care at home, our department staff arranges home visits by primary care doctors and nurses. For patients being transferred to local institutions, our staff provides assistance both to general hospitals and hospice care units.

Home Care Support (Home Care Support clinic): Our Home Care Support Clinic, which offers home care support to our outpatients, has been running since January 2003. The clinic supports the implementation and coordination of home care services, and refers outpatients requesting hospital admission to other hospitals or facilities.

Consultation by Social Worker (Consultation on Recuperation): Our consultation service provided by social workers has been running since 2012. Our social workers mainly consult enquiries regarding patient recuperation.

Transferring out patients to local institutes: Aiming to defining the distinction of the medical role between the University Hospital and local institutes and facilitate transferring our outpatients to them, the proportion of such transferring patients to first-visit patients keeps more than 80%.

Teaching activities

We educate undergraduate students of the Medical Social Working and Welfare of other university.

Research activities

Our research field covers investigating appropriate patient numbers for assistance to inpatients upon discharge in the University hospital; and investigating how to assist working and job in patients with severe illness.

Department of Cancer Resource Center

Chief

Sachiyo Nomura, M.D.,Ph.D.

Associate chief

Takako Wakeda, M.D.,Ph.D.

Counseling staff

Megumi Yasuda, 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.

References and Presentation

1. Makeup as care for changes in appearance due to cancer treatment. FRAGRANCE JOURNAL 22 Research and Development for Cosmetics, Toiletries & Allied industries Special issue p126
2. Inadequacy of Appearance Care for cancer patients in Japan. MASCC/ISOO Annual Meeting on Supportive Care in Cancer 2019, HYATT REGENCY SAN FRANCISCO

**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.

Assistant Professor

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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 decomposes fatty droplets resulting in controlling the

progression of obesity. However, when this process undergoes effectively and excessively under the obese condition, oppositely to control the progression of obesity, chronic inflammation of adipose tissue and insulin resistance are triggered and Type II diabetes and atherosclerosis are worsen.

Moreover, because AIM binds to IgM in bloodstream, it leads to production of various auto-antibodies, especially under the obese condition. This suggests that the obesity is the cause of autoimmune disease. Other studies showed that liver disease, cancer, and kidney disease worsen under low concentration of AIM. It is suggested that the concentration of AIM in bloodstream differentiates the outcome and the risk of getting various diseases.

The project was accepted for Advanced Research and Development Programs for Medical Innovation, Leading Advanced Projects for medical innovation (LEAP) 2019, 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.

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

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Laboratory of Structural Physiology

Professor

Haruo Kasai, M.D., Ph.D.

Lecturer

Sho Yagishita, M.D. Ph.D.

Research Associates

Yusuke Iino, M.D. Ph.D.

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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 20 members of our laboratories in the March of 2019 are Haruo Kasai, Sho Yagishita (Lecturer), Kazuhiko Ishii (Research Associate), Kenji Yamagushi (Project Researcher), Hasan Ucar (Project Researcher), Yusuke Iino (Research Associate), Mio Tajiri (D4), Takeshi Sawada (D4), Yuichi Morimoto (D4), Toshiaki Kume (D3), Hongyu Amy Chang (Master course student, M2), Hitoshi Okazaki (Medical Intern), Monami Nishio (Medical school student, M2), and as technical staffs, Haruka Ohno,

Arisa Kurabayashi, Yuki Sakata, Masayoshi Asaumi, Rie Yonemoto 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. 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, Kasai, 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, Kasai, 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, Kasai 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 psychosis. 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) The D2 system and new computational models.

To corroborate the experimental studies we first examined the intracellular molecular machinery that shuttles dopamine signals from cell receptors to changes in specialized cell compartments called postsynaptic spines, the small protrusions on cell dendrites that enable intercellular communication (Ref. 6). In a deep brain area called the ventral striatum reside two types of cells with dopamine receptors, called D1 and D2 that handle, respectively, reward and risk (or punishment) learning. The researchers built a detailed molecular model of the protein cascade that resides in D1 and D2 cells. D1 and D2 cells learn the language, so to speak, of dopamine pulses and dips, respectively, to enlarge their spines in the form of memory. Interestingly, the model reveals the role of a protein enzyme called adenylyl cyclase type 1 in “contingency detection” where two signals arrive on a single cell in the same time window, allowing the cell to learn what the researchers call “temporal contiguity” or the pattern of dopamine in reward learning.

In the second study (Ref. 5), we zoomed out to the animal behavioral level by developing a model of reinforcement learning that has D1-like and D2-like cells in a multilayered neural network designed after a form of network configuration called an extreme learning machine (ELM). The model, called OVaRLAP, contains computational elements similar to the D1 and D2 neurons that are known to process respective positive or negative dopamine reward prediction error signals. These distinct signals are thought to drive two different patterns of reinforcement learning, generalization and discrimination, that were recently validated by the group in Iino et al. (2020) *Nature*. The team tested the performance of OVaRLAP against a computer game called the painful grid world navigation task where the agent controlled by the model has to avoid the “painful” walls of a

maze to move to safety.

OVaRLAP showed high performance due to a fast generalization resulting from the D1- and D2-like elements in the network’s final layer (Ref. 5). However, in a similar game played with impairment in discrimination learning by D2-like elements and background noise applied to the ELM, the model surprisingly failed to generate proper behavior. We suggest this aberrant behavior might mimic mental conditions such as schizophrenia related to the intrinsic design of the dopamine reward system and its powerful generalization and discrimination capacity, where high performance is associated with a higher risk of system breakdown. Intriguingly, the results imply that future neuro-inspired AI might inherit both high cognitive capacity and mental disorders from their biological antecedents, a cautionary note. Together, the two studies show that multiscale modeling, from molecules to behavior, can reveal insights not only on dopamine reward learning but on the human brain itself.

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Laboratory of Biomedical Equipment and Biomaterials

Professor

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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 Bioengineering 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.

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 has been analyzed to quantify surgical skills. For example, an image processing method to track the needle pose in the microscopic view has been developed to quantify the manipulation skills of expert surgeons. VR surgical simulators have also been developed for autonomous surgical process modeling (SPM).

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

Robots to assist scientific experiments, such as dissection of mouse, has been designed. Collaboration is planned with mathematicians, AI researchers, robot researchers, and scientists.

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Laboratory of Clinical Biotechnology

Professor

Yuichi Tei/ Ung-il Chung, M.D.,Ph.D.

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Hironori Hojo, Ph.D

Assistant Professor

Hiroyuki Okada, M.D., Ph.D

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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 aforementioned biomedical professionals.

Research

We pursue two scientific interests with a particular focus on skeletal tissues (bones and cartilage): (1) the manipulation of progenitor cell differentiation and proliferation based on the understanding of molecular mechanisms underlying cell fate specification, and (2) the development of novel biomaterials fulfilling the characteristics required for *in vivo* use as scaffolds. We aim to develop novel systems for skeletal tissue engineering and regenerative medicine in which cell differentiation and proliferation are directly regulated *in situ*. The following four projects are ongoing.

1. Understanding of epigenome dynamics and gene regulatory networks during cell fate specification processes

Organogenesis depends on cell fate specification and the subsequent differentiation and maturation of specified cells. Gene transcription underlies a series of processes; appropriate genes are transcribed with appropriate amounts and at the appropriate timing for inducing cell activities and characteristics. In this context, the epigenome works as a main switch for gene expression. Transcription factors, which bind to the genome in a sequence-dependent manner, in turn increase the amount of transcripts, in a manner that is analogous to turning up the volume of a radio.

Against this background, we seek to understand the mechanisms of cell fate specification, cell differentiation, and cell maturation during skeletal development with a particular focus on epigenome dynamics and genomic targets of transcription factors. We also plan to apply the knowledge gained to the development of regenerative therapies for skeletal tissue defects. Here we rely on the following approaches: (1) observations of intracellular events by direct and comprehensive techniques, (2) the construction of hypotheses driven by these observations, and (3) verification of the hypotheses. Thus, the approach starts with the collection of genome-scale data on gene expression, epigenome, and transcription factor binding sites by taking advantage of next-generation sequencers. The data are analyzed by bioinformatics approaches, leading to the construction of a new biological hypothesis. Each hypothesis is verified by molecular-biological approaches and mouse genetics. With this research strategy, we are investigating the regulatory landscape on the genome that determines the specification of bone- and cartilage-forming cells, osteoblasts and chondrocytes, respectively, and their phenotypes. A series of studies reveals transcriptional networks that mediate pluripotency and the differentiation of pluripotent stem cells (*Stem Cells* 31:2667, 2013), epigenome dynamics and modes of action of master transcription factors that specify osteoblasts and chondrocytes, and the gene regulatory networks mediated by those master transcription factors (*Cell Reports* 12:229, 2015; *Developmental Cell* 37:238, 2016; *Development* 143:3012, 2016; *Trends in Genetics* 32:774, 2016;

Regen Ther 6, 100-107, 2017; *Int J Mol Sci.* 20(24). pii: E6324, 2019; *Bone.* 137:115458, 2020). 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). 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.

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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 (two for the doctoral course and one for the master course), four external researchers, and one research assistant conducted the researches together during the year of 2020.

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 A₂ (PLA₂) family, we aim to elucidate the molecular pathophysiology of diseases (*e.g.* metabolic and immune diseases) that are problematic

in modern society. Based on this, we will promote the research of Quality of Lipids (QOL) for Quality of Life (QOL) and aim at building a theoretical foundation for diagnosis, prevention and treatment of diseases involving alteration of lipid metabolism.

1) Metabolic diseases

We previously reported that PLA2G5 (sPLA₂-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 (sPLA₂-IID), secreted from M2-like macrophages in white adipose tissue, releases ω 3 polyunsaturated fatty acids (PUFAs) to promote cold-induced adipocyte browning and thermogenesis (Sato et al, *Cell Rep*, 2020). In addition, we have recently found that sPLA₂-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 (iPLA₂ γ), which acts as PLA₁/A₂, 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 (sPLA₂-IIF), which is specifically expressed in epidermal keratinocytes, mobilizes lysoplasmalogen, a unique lysophospholipid that promotes epidermal hyperplastic diseases such as psoriasis and skin cancer (Yamamoto et al, *J Exp Med*, 2015), and that PNPLA1, a member of the intracellular iPLA₂ 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). Furthermore, by phenotypic screening (with perturbation of skin barrier function as a readout) using a series of PLA₂ knockout strains, as well as by gene expression profiling of PLA₂-related genes in mouse and human skins, we have identified several PLA₂s that appear to be linked to the regulation of skin homeostasis and diseases.

Among these PLA₂s, PLA2G4E (cPLA₂ 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.

PLA2G3 (sPLA₂-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, *Pla2g3*^{-/-} mice display more severe atopic dermatitis-like symptoms with increased expression of type 2 cytokines and chemokines (IL-4, IL-13, IL-33, TSLP, and CCL17), serum IgE levels, eosinophil infiltration, and scratching behavior. Global or skin-specific deletion of EP4 (PGE₂ receptor) or FP (PGF_{2 α} receptor) largely if not solely recapitulate these phenotypes, suggesting that the PLA2G3-driven PGE₂-EP4/PGF_{2 α} -FP signaling in keratinocytes plays an important role in skin barrier formation and thereby

skin homeostasis, perturbation of which leads to exacerbation of atopic dermatitis.

3) Allergic and other immunological diseases

We previously reported that PLA2G3, an sPLA₂ isoform secreted from mast cells (MCs), promotes MC maturation by driving the paracrine PGD₂ circuit in cooperation with microenvironmental fibroblasts (Taketomi et al, *Nat Immunol* 2013) and that PAF-AH2, a unique PLA₂ that hydrolyzes oxidized phospholipids, ensures optimal MC activation and thereby allergic responses through producing unique EPA/DHA metabolites (ω 3 epoxides) (Shimanaka et al, *Nat Med* 2017). We have recently confirmed the role of PLA2G3 in MCs by demonstrating that mice lacking PLA2G3 specifically in MCs, like those lacking the enzyme in all tissues, have immature MCs and display reduced local and systemic anaphylactic responses. In addition, MC-specific *Pla2g3*-null mice display an aggravated contact hypersensitivity (CHS), which is phenocopied by MC-specific deletion of hematopoietic PGD₂ synthase. Thus, MC-secreted PLA2G3 promotes MC maturation via PGD₂, thereby facilitating acute anaphylactic reaction and limiting delayed CHS response (Taketomi et al, *Cells* 2021). Furthermore, we have recently found that PLA2G3 is also coupled with another lipid mediator, lysophosphatidic acid (LPA), which acts in concert with PGD₂ to facilitate MC maturation.

PLA₂ subtypes that regulate T cell immunity are unknown. By transcriptional and functional screening of PLA₂ enzymes expressed in T cells, we have found that PLA2G12A (sPLA₂-XIIA), an orphan sPLA₂, 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 $\gamma\delta$ T 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) Cancer

Despite the restricted intestinal expression of PLA2G2A (sPLA₂-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. These results highlight a new aspect of PLA2G2A as a modulator of gut microbiota, perturbation of which affects distal skin responses (Miki et al, *JCI Insight*, in press).

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 sPLA₂-driven lipid metabolism. Hydrolysis of EV phospholipids by PLA2G10 (sPLA₂-X), which is induced in macrophages of Epstein-Barr virus (EBV) lymphoma, increases the production of fatty acids, lysophospholipids and their metabolites. sPLA₂-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 sPLA₂ inhibitor, while treating the mice with sPLA₂-modified EVs can reverse this phenotype. Overall, the sPLA₂-driven EV modification promotes tumor development (submitted).

5) Infectious diseases

PLA2G2D expressed in dendritic cells and M2 macrophages attenuates anti-viral Th1 immunity by supplying ω 3 PUFAs and PGD₂. In collaboration with a foreign group, we have reported that *Pla2g2d* deficiency protects mice from pneumonia caused by coronavirus infection (Vijay et al, *J Exp Med* 2015; Zheng et al, *J Clin Invest* 2021; Roy Wong et al, *bioRxiv* 2021). Therefore, PLA2G2D may be an attractive drug target for treatment of COVID-19.

6) Neuronal diseases

Mutations in the *PNPLA6* gene cause neuronal and retinal degeneration such as hereditary spastic paraplegia (SPG39), Boucher-Neuhauser syndrome, Oliver-McFarlane syndrome, and Laurence-Moon syndrome. However, it is unclear how *PNPLA6* mutations lead to these disorders. We have confirmed that PNPLA6 acts a phospholipase B (PLA₁/A₂ + 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. 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.

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+IFN γ -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 Metabolic 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).

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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, a project academic support specialist, 2 assistant laboratory animal technicians, and 4 assistant clerks. 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 1023 at the end of academic year 2020.

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. We found that expression of FMRP was reduced in these mutant marmosets. There is an “mGluR5 hypothesis” that symptoms of fragile X syndrome are caused by activation of mGluR5 pathway. To examine the mGluR5 hypothesis in non-human primates, we generated *FMR1/GRM5* double mutant marmosets. We will analyze *FMR1* mutants and *FMR1/GRM5* double mutants to examine the mGluR5 hypothesis.

2. Analysis of Group I mGluRs

Metabotropic glutamate receptor subtype 1 (mGluR1) and subtype 5 (mGluR5) are coupled to trimeric G protein Gq, shared ligand specificity and homologous amino acid sequences, and constitute group I mGluRs. They exhibit nearly complementary distributions, spatially and temporally, throughout central nervous system. Significance of complementary expression of the receptors and their functional redundancy are still unknown. Therefore, we have generated “mGluR5-rescue” mice, in which mGluR5 is specifically expressed in cerebellar Purkinje cells in mGluR1-KO background. We found that the mGluR5-rescue mice showed apparently normal motor coordination, although mGluR1-KO mice show severe ataxia. Furthermore, we found that abnormal synapse elimination at climbing fiber synapse in mGluR1-KO mice is rescued by ectopic expression of mGluR5 in Purkinje cells. These results indicate a functional redundancy between mGluR1 and mGluR5 in cerebellar Purkinje cells.

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Laboratory of Molecular Radiology

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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 SYCP3-expressing cells are hypersensitive to radiation and cisplatin and are characterized by increased aneuploidy. As these phenotypes are consistent with those of defective HR, we screened the molecule that co-localizes with SYCP3 by immunofluorescence. Consequently, we identified that the tumor suppressor BRCA2 co-localizes with SYCP3. We also confirmed that these proteins form a complex. Furthermore, we found that binding of SYCP3 to BRCA2 inhibits the HR repair activity mediated by binding of BRCA2 to Rad51.

Since cells with BRCA1 or BRCA2 mutations are hypersensitive to PARP inhibitors, their clinical trials are internationally ongoing. However, the problem is that the application of the trial is limited due to low incidence of their mutations. Our findings implicate that SYCP3-expressing cancers, even if they do not harbour BRCA mutations, are sensitive to PARP inhibitors, providing novel insight into cancer therapy based on the synthetic lethal approach in which both two pathways essential for cell viability are disrupted by an intrinsic genetic alteration and a specific pathway inhibitor.

SYCE2, a component constituting the synaptonemal complex, is also expressed at varying levels in somatic cells. SYCE2 insulates heterochromatin protein 1 α from trimethylated histone H3 lysine 9 to promote ATM-dependent DNA double-strand break repair. This finding suggests that SYCE2 plays a role in the link between the nuclear microenvironment and the DNA damage response in somatic cells.

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 Rad51 and 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 mediated 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.

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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.

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The International Research Center for Medical Education (IRCME)

Department of Medical Education Studies

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History and organization

International Research Center for Medical Education, established in 2000, had functioned as a center for the whole university and kept relations with Graduate School of Medicine in various ways. IRCME became an affiliated center for education and research under the control of Graduate School of Medicine since April 2013. IRCME previously consisted of two departments of International Cooperative Study in Medical Education, and Planning & Cooperation for International Cooperative Projects and Information on Medical Education. Names of two new departments are Department of Medical Education Studies and Department of International Cooperation for Medical Education.

The mission of Department of Medical Education Studies includes promotion of medical education not only in Faculty of Medicine of the University of Tokyo but also of the whole country. Specific contents are as follows:

- (1) Research in medical education and dissemination within and outside of the University

Medical and health professions education needs to continue revisions to meet health care needs of the country or the region. However, since every country or region has different culture or social system, experiences to apply updated evidence to the real settings to revise the system.

- (2) Support to undergraduate and postgraduate education in the University

Through the support to education in Faculty of

Medicine and the University Hospital, we show the effectiveness of such teaching practice and apply it to other medical schools in Japan for future reform.

Activities

This department promotes research related to medical education field. As the studies of medical education develop very rapidly all over the world, the department expands research to construct theories and emphasizes activities of educational practice or improvement.

In the University, this department provides information and members as to the education of Faculty of Medicine in such as academic affair committee, medical education reform working group, and clinical clerkship. Moreover, the department offers educational activities such as PBL (problem-based learning) and clinical skill practical training. The department operates OSCE (objective structured clinical examination). The department also runs and manages “Tsutsuji no kai” under the consortium with Tokyo Medical Dental University to develop simulated patients indispensable for education of medical interview.

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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 umbrella of Graduate School of Medicine since April 2013. IRCME currently consists of Department of Medical Education Studies and Department of International Cooperation for Medical Education (ICME).

Department of ICME is a handling comprehensive practices and research, both in the field of international cooperation in health-professions-education-related area and in the field linking policies and actual practices such as international health, community medicine, and general practice. Specifically, it is as follows.

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) 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.

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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 2020, two international joint research projects and an industry-government-academia research projects were undertaken. In addition, 79 original English articles were published.

Executing Innovative Research

1. International Invited Faculty

In 2020, we appointed 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 2020, two PD researchers participated in this program, and completed the program.

3. Other Universities’ Young Researchers

In 2020, our PD seminars and lectures were opened to young researchers from other universities, and by the end of the year, a total of 1953 participants attended. Furthermore, we conducted research consultations or technical assistance and training for two young researchers.

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

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Office of International Academic Affairs

Head

Shinichi Sato

Assistant Professors

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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 2020-21 academic year (1 April 2020 through 31 March 2021).

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 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 the cancellation of elective clerkships scheduled in 2020-21.

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, University of Chicago, 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. Arrangements to send three students to Harvard University from April to July 2021 for one to two months of research were also cancelled.

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 2020-21, the OIAA assisted in preparing Medical Student Performance Evaluations for two applicants.

2. International Academic and Research

Agreements

During the 2020-21 academic year, a new interdepartmental agreement for the exchange of medical students was signed with Karolinska Institute, and the interdepartmental agreement with the University of Munich was renewed.

3. Education and Research Activities

Dr. Yosuke Matsumiya and 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 taught "Basic tools for Population/Public Health Research" and served as a lecturer in the School of International Health, where she supervised graduate students and conducted research on international health.

Publications

1. Kikuchi K, Gyapong M, Shibamura 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.
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MD Scientist Training Program

Professor and Director

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

Lecturer

Yuki Sugaya, M.D., Ph.D.

Assistant Professor

Kei Takahashi, 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) and Prof. Masahide Kikkawa (2011-2014), the Program currently consists of its director Prof. Haruhiko Bito and 2 staff members, Yuki Sugaya (lecturer) and Kei Takahashi (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, and has received governmental funding support to dramatically boost its activities.

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 2020, the pandemic of COVID-19 prevented students from doing research abroad. Instead, 7 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 online retreat was held on February, 13, 2021 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 on, 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. Four celebrated MD scientists presented their research achievements and carrier path in a joint forum of this meeting.

The MSDTP also currently cooperates with 10 other universities in eastern Japan to organize annual research students' retreats. However, in 2020, annual summer retreats was canceled due to the pandemic of COVID-19.

Activities (2020)

The number of registered students: 116 (3rd and 4th grade: 64, 5th and 6th: 35)

Lectures for students in Years 1 and 2

Introduction to Medical Biology: 13 lectures

Group reading of Molecular Biology of the Cell: 12 lectures

Seminar for students (in Year 3 or above)

Journal Club for basic medical research: 6 lectures

Medical Research Communications: 69 lectures

Presentation of research progress: 1 times at the online retreat of MD scientist training program in the University of Tokyo

The number of students receiving travel supports for research : 7 (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: 7 (the Dean's Prize and the Satoshi Arima memorial fellowship were awarded to 2 and 1 student, respectively)

Museum of Health and Medicine

Director

Kazuhiko Ohe

Associate

Atsushi Kitade

Homepage <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 400m² areas, including about 70m² of a permanent gallery and 230m² of special exhibition rooms.

The aims of the Museum are to: (1) provide health and medical information to the public, (2) educate students studying medicine, health care services and related areas, (3) research the history of medicine and health care through archives, instruments and technology, and (4) preserve and investigate valuable medical archives and instruments, etc.

In addition to the permanent gallery exhibiting accomplishments related to the School and the Hospital and its contributions made to modern and

contemporary development in Japan, a feature of the exhibitions is that a large space has also been set aside for special exhibitions to promote understanding among the public regarding the latest advances in medical science and health care. Planning and supervision of the permanent exhibition and special exhibition is done with the cooperation of the various research units within the School and the Hospital, other departments within the University, industry, and museums. Special exhibitions will be changed several times a year.

The first permanent exhibition since the opening of the Museum was a display of medical texts and instruments from the early Meiji era, an Ishihara’s Color Blind Test Chart and a gastroscope developed at the University. The first special exhibition was related to the beginnings of the School and the Hospital, Entitled “the Challenge to Infectious Diseases”. It introduced the history of vaccinations against smallpox, research into infectious diseases conducted in the University and by its graduates since the Meiji era (1868-1912), and the latest knowledge about infectious diseases. The second was “the Secret of Vessel System”, which introduced the circulatory system. The third “diagnosis of cancer”, the fourth “Our brain”, the fifth “Locomotive syndrome”, the sixth “Diabetes Mellitus”, the seventh “Pediatrics”, the eighth “Forensic Medicine”, the ninth “the Colon” followed, the tenth “Virus”, the eleventh “Kidney” and the special exhibition “Mental Diseases”.

In April 2019, we reopened our museum in the South Clinical Research Building of The University of Tokyo Hospital.

Since the opening of the Museum, more than 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.

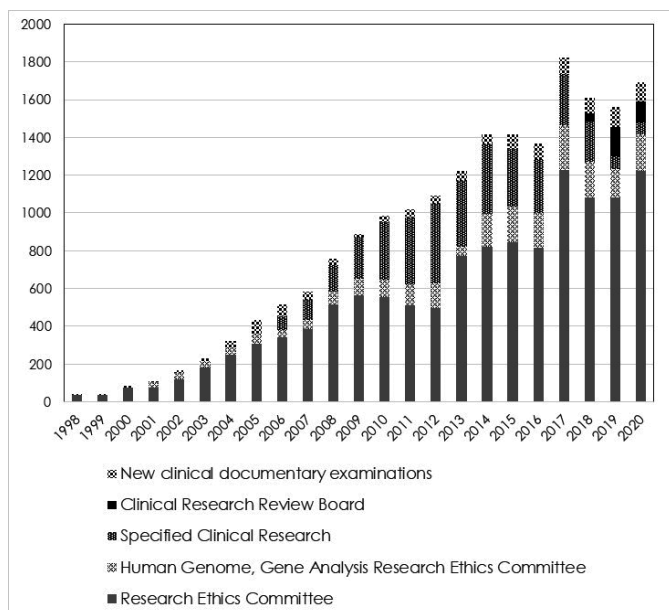
Activities

- 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 2020

- Research Ethics Committee (except for clinical trial, GCP):
399 new applications, 1047 minor alterations of approved studies
- Clinical Research Review Board:111
- New clinical documentary examinations: 102



Research activities

At present, OHRS is a business section. For more information about the research, see the contents of Department of Biomedical ethics, which is a cooperative department.

Though OHRS adopts various inclusive applications, the number of studies applied to and reviewed by ethics committees over the last several years is on the increase. 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 2020 with 3359 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.

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

Presently the “Research of the coherence between the students’ daily life and the outcome at the graduation” is being conducted. The results-in-progress were released in the domestic and international conferences of medical education in 2018 and 2019, being followed in 2020. This research is also developing into multiple institutional investigation.