

# 東京医学

THE TOKYO JOURNAL OF MEDICAL SCIENCES

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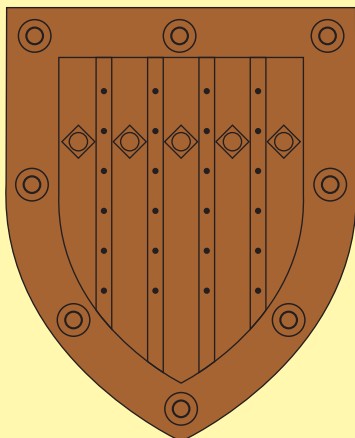
October 2020

Vol.141

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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 2019 — March 2020**



共同編集 東京医学会・東京大学医師会・東京大学医学部

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東京医学
Tokyo J. Med. Sci.

ANNUAL REPORT OF THE GRADUATE SCHOOL OF  
MEDICINE

THE FACULTY OF MEDICINE  
THE UNIVERSITY OF TOKYO

REPORTS FOR THE PERIOD April 2019-March 2020

## **Introduction**

This is volume 141(the edition of year 2020) 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.

Nobuhito Saito, Dean  
Graduate School of Medicine and Faculty of Medicine  
The University of Tokyo

October, 2020

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## History

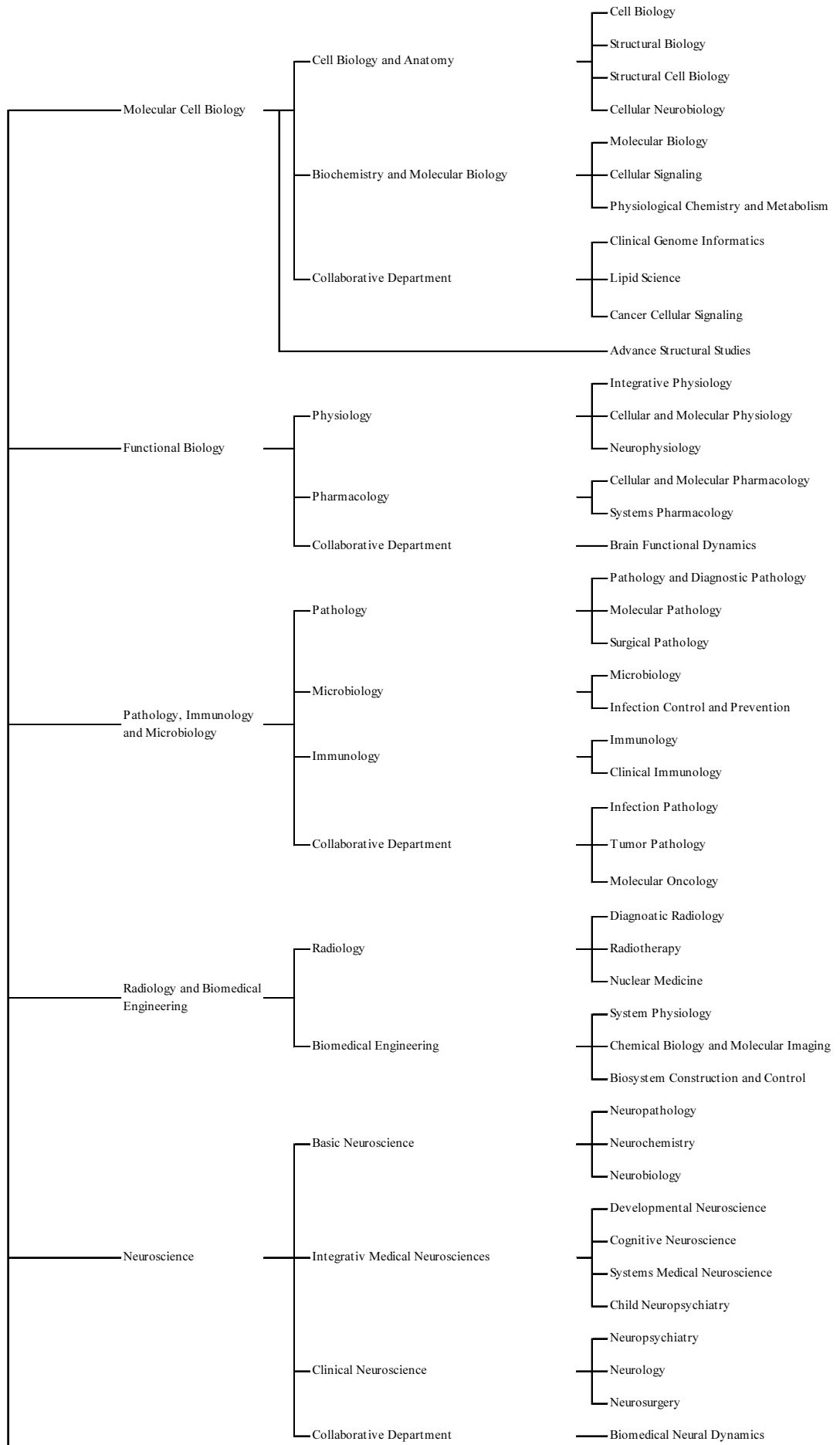
- 1858 May Practitioners, trained in Dutch (European) medicine in Edo (Tokyo), laid out money to establish the Shutojo (vaccination center) in Kanda Mitamagaiké.
- Nov. Shutojo was destroyed in a fire that had spread from Kanda Aioicho. Shutojo continued its operations at other sites such as the residence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

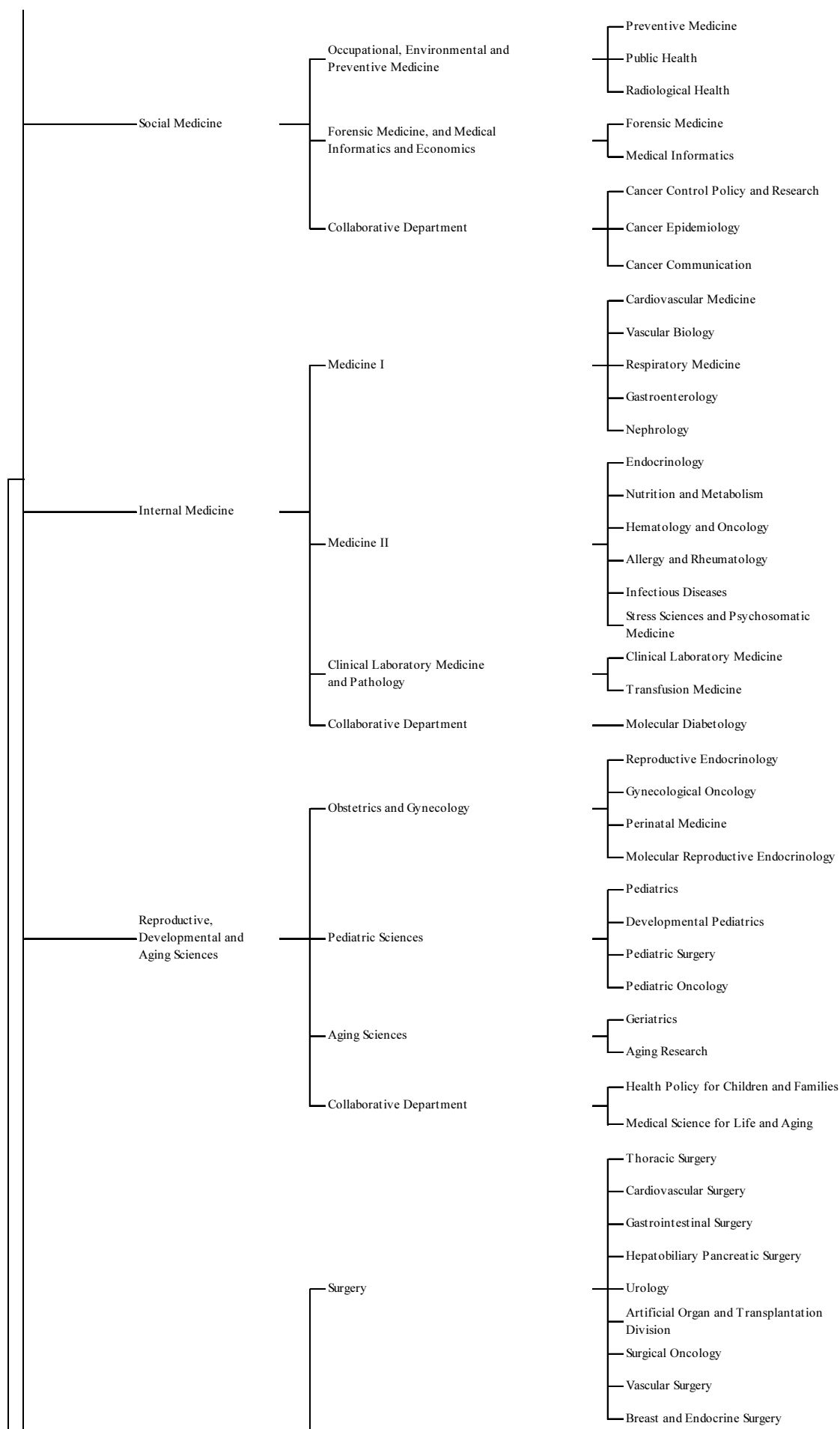
- Jul. The Graduate School was founded, and the Division of Medical Doctor Biological Science was established. The Brain Research Laboratory became the Brain Research Institute of the Faculty of Medicine.
- 1956 Apr. The Midwives School was established.
- 1958 Apr. The Division of Pharmaceutical Sciences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

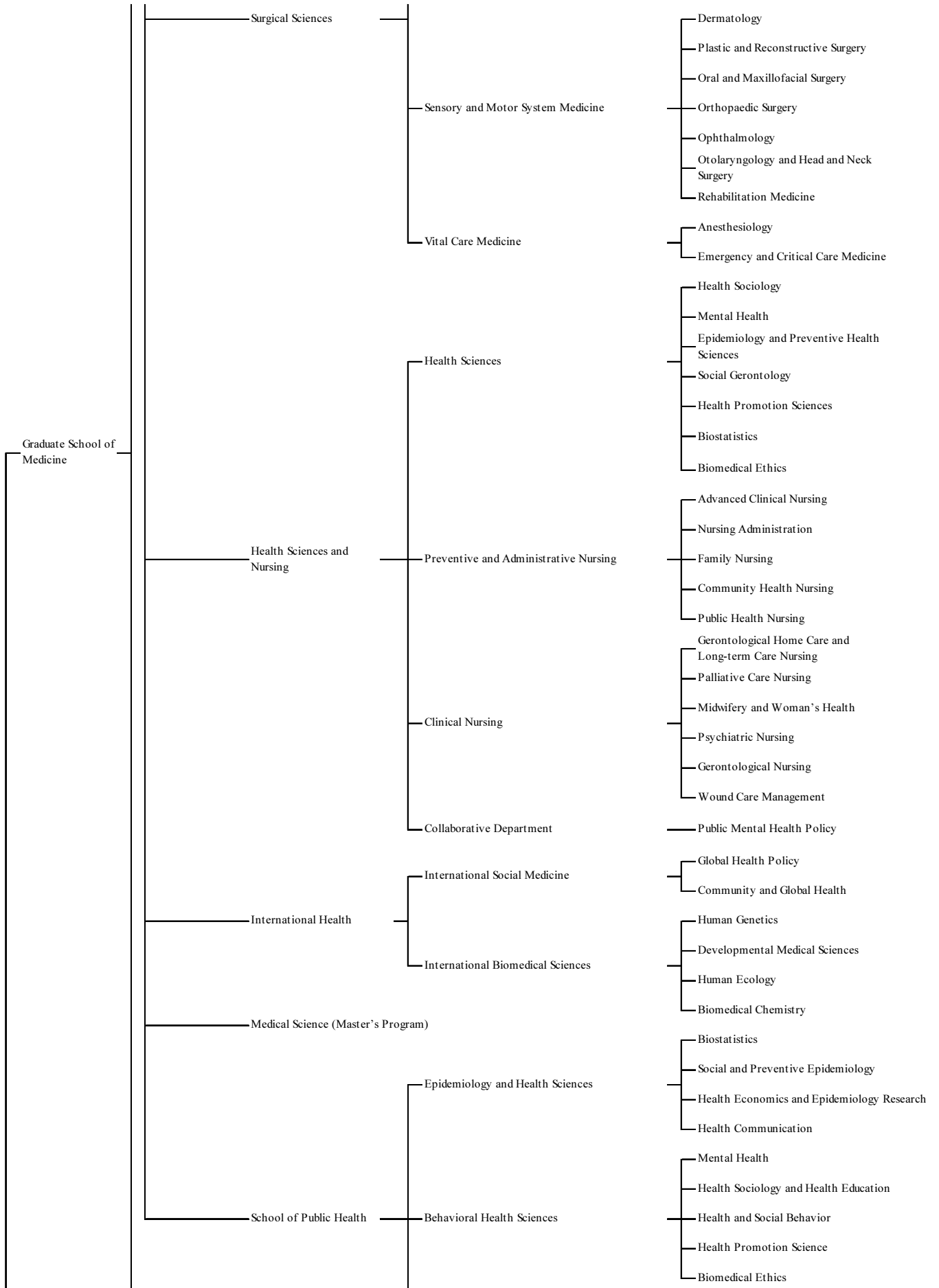
- 2000 Apr. The International Research Center for Medical Education was established (A shared facility for education and research).
- 2001 Apr. The University Branch Hospital was united with the University Hospital.
- 2002 Mar. Nursing School and Midwives School was Closed.
- 2002 Mar. Experimental Building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

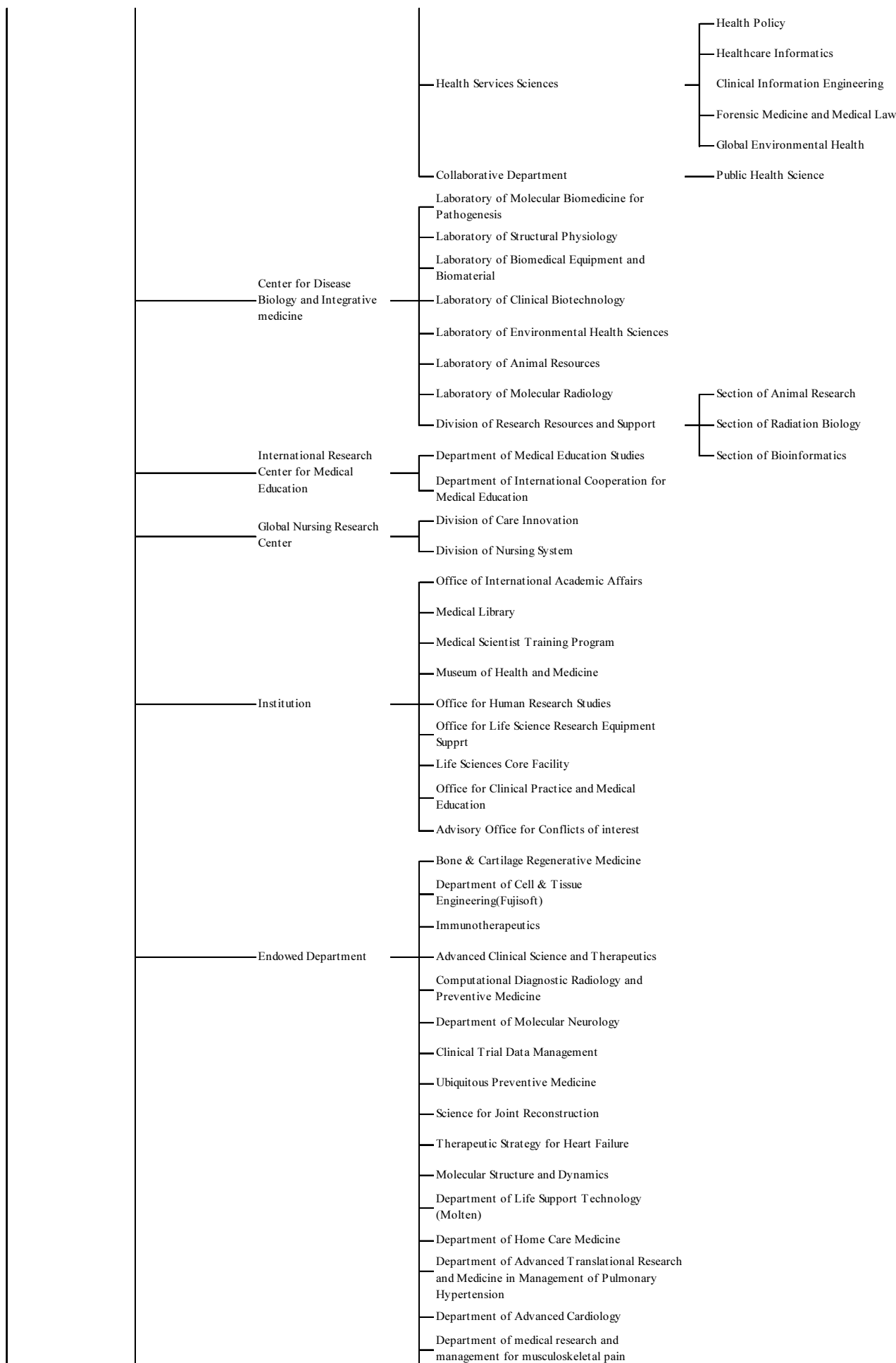


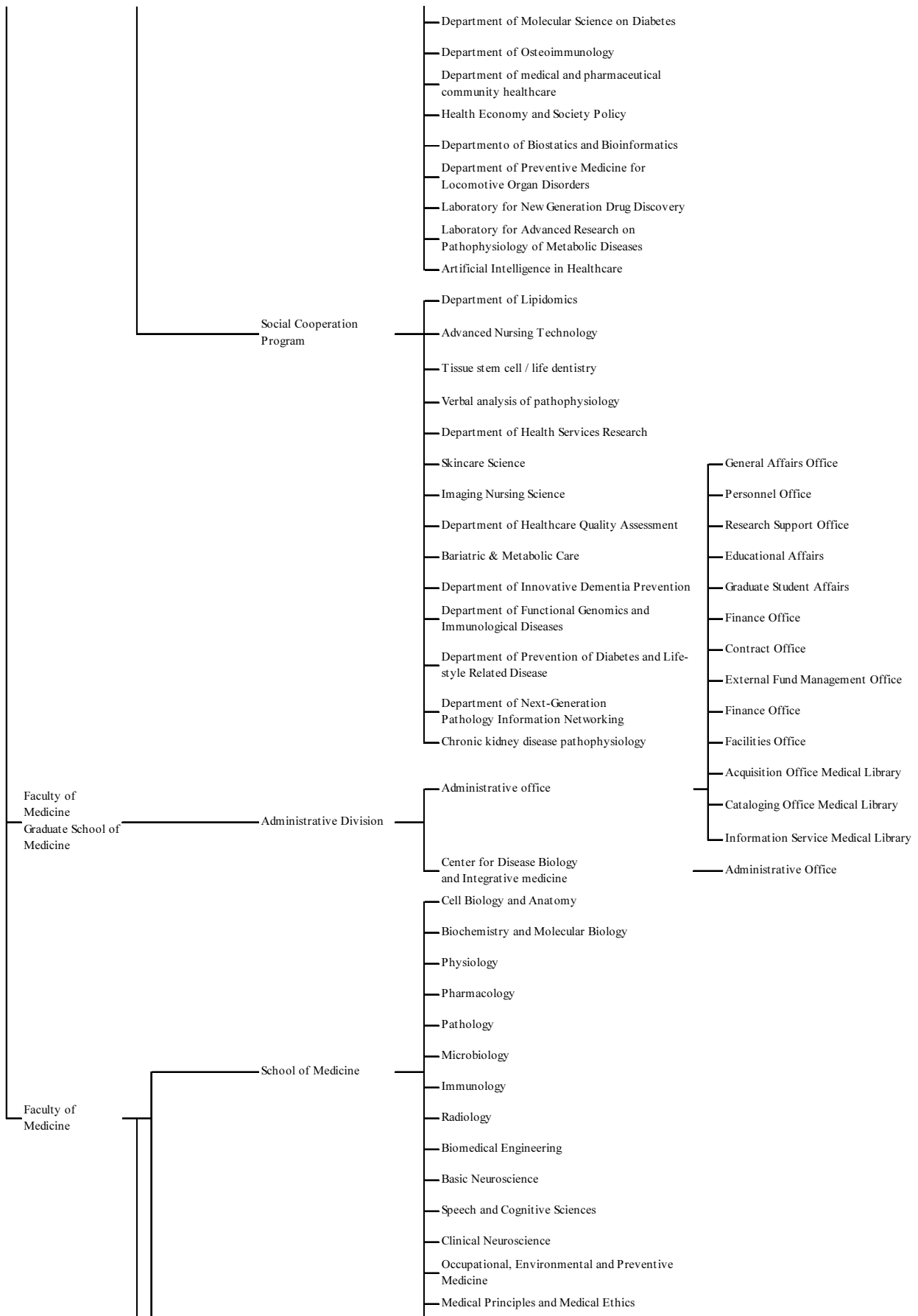
### Organization Chart

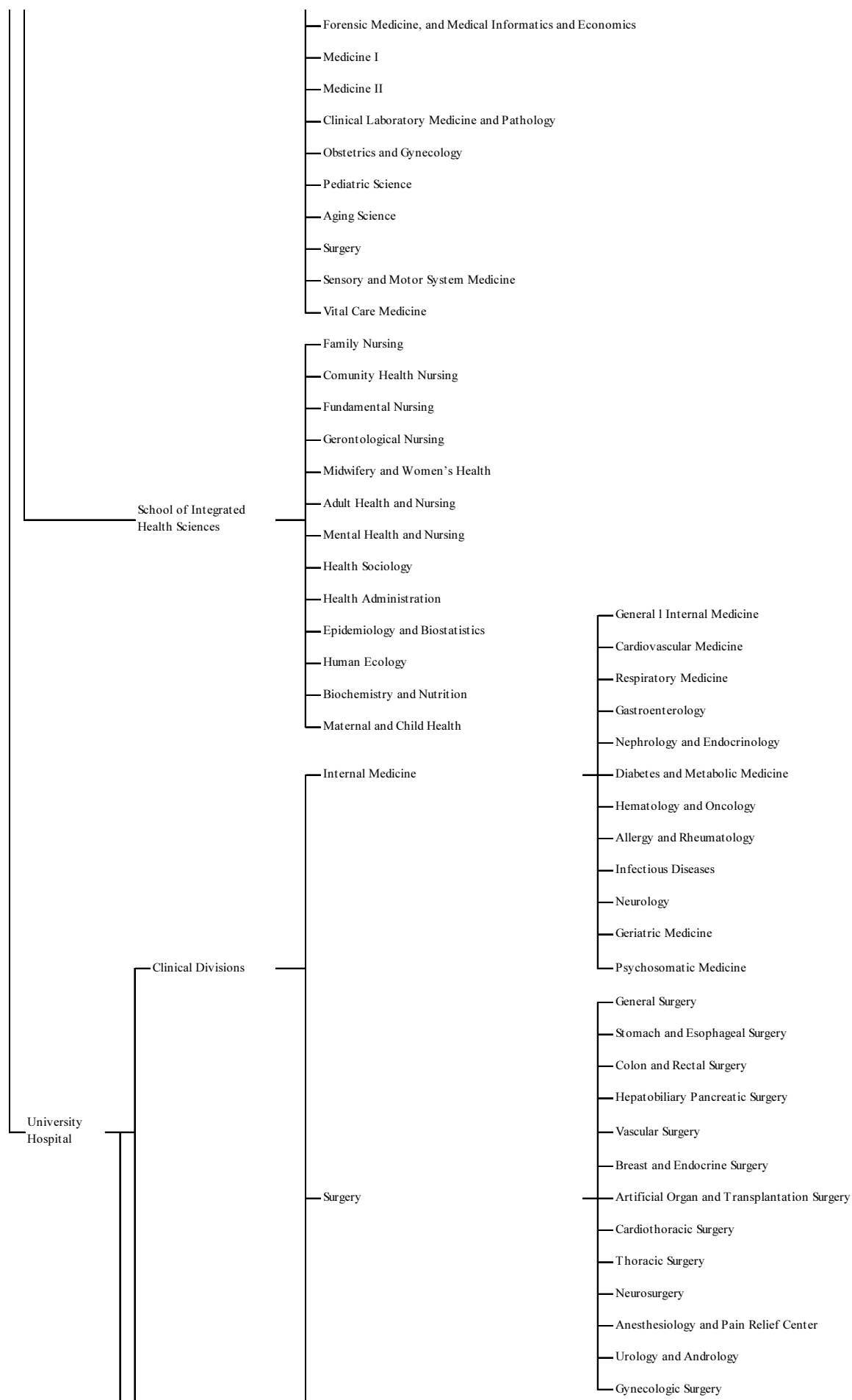


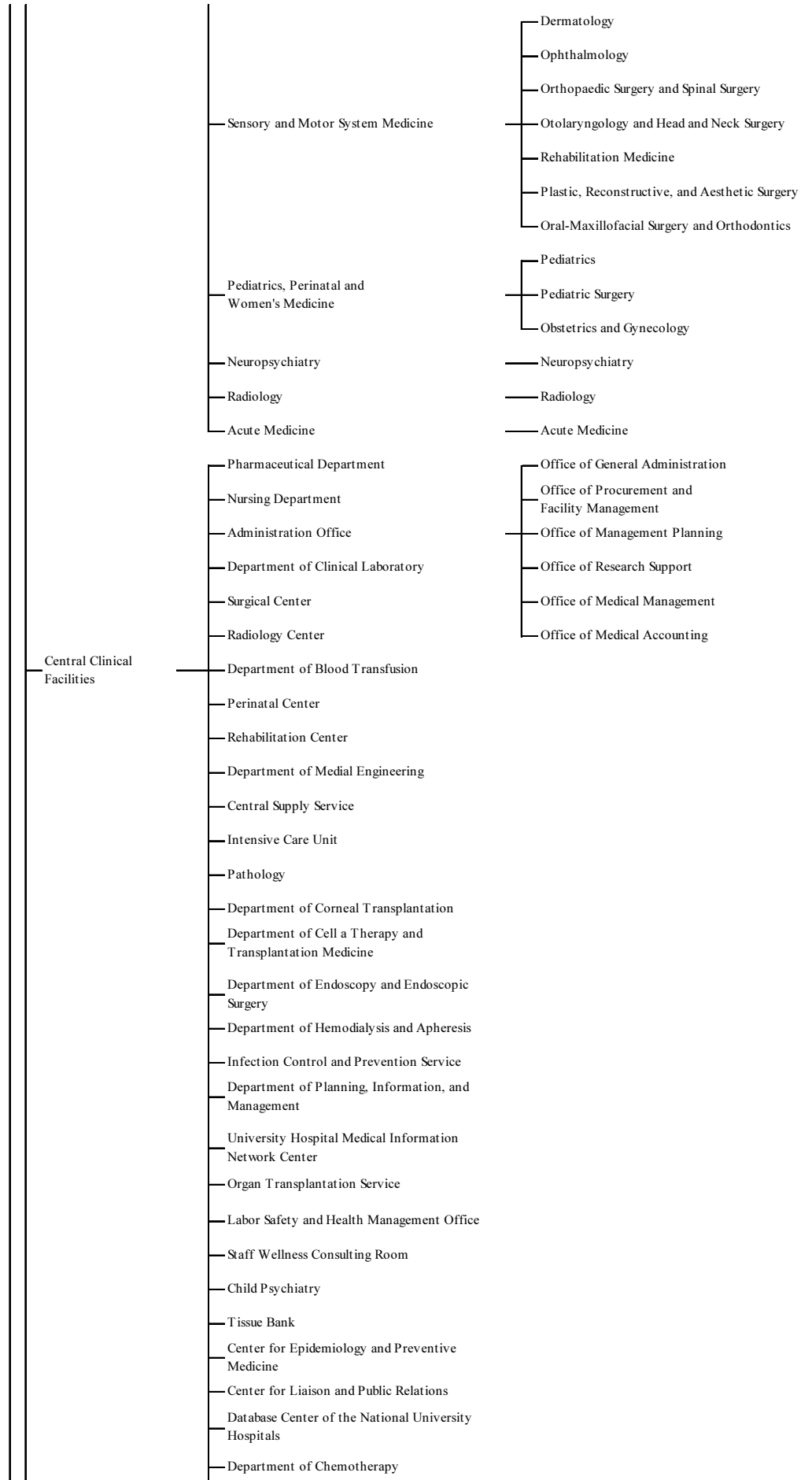


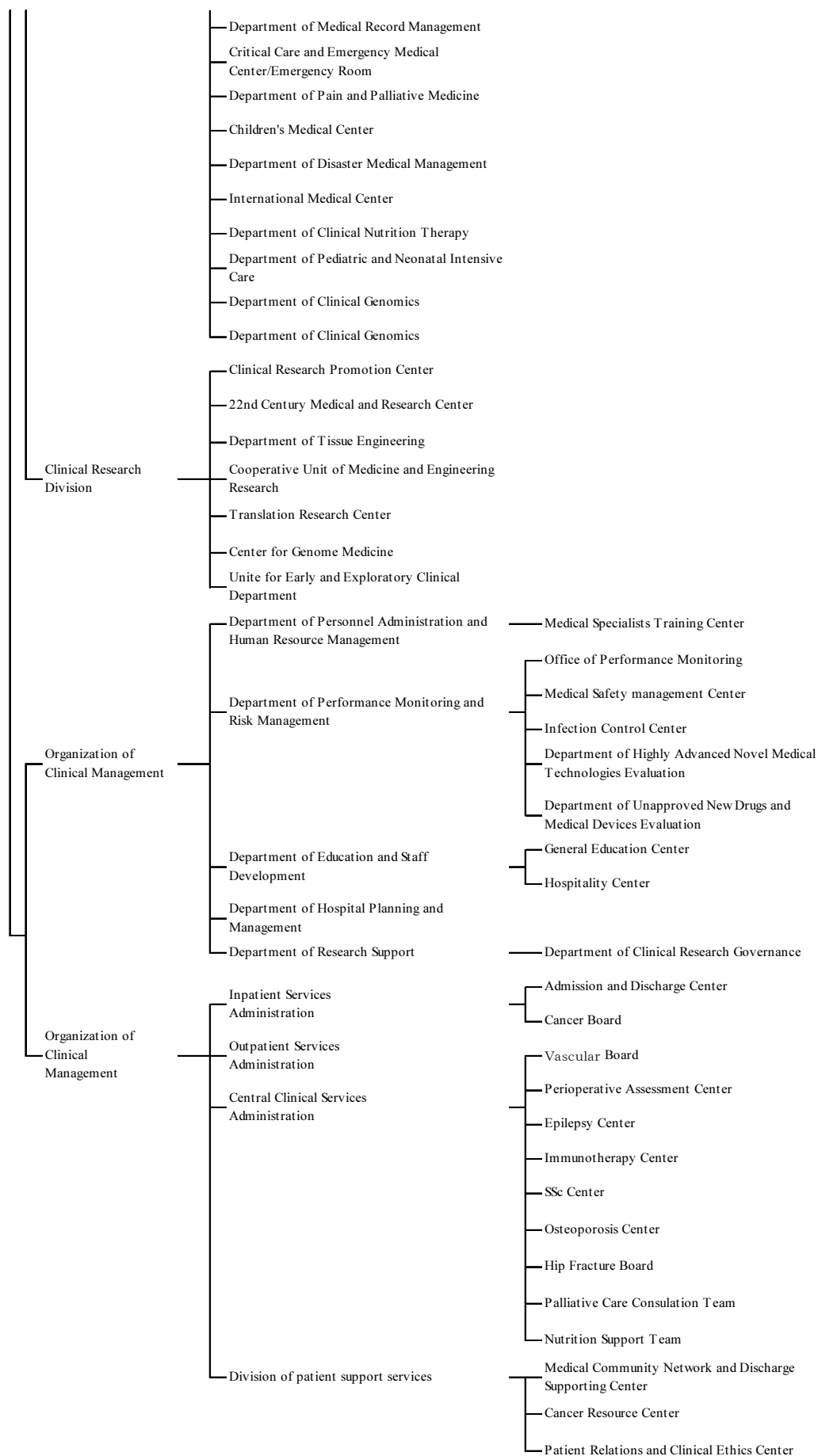














## **Teaching, Research, Secretarial and Administrative Staffs**

### **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	DANEV RADOSTIN

#### **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
<b>Neuroscience</b>		
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
<b>Social Medicine</b>		
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
<b>Internal Medicine</b>		
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
<b>Reproductive, Developmental and Aging Science</b>		
Department of Obstetrics and Gynecology	Professor	Tomoyuki Fujii
	Professor	Yutaka Osuga
Department of Pediatric Science	Professor	Akira Oka
Department of Pediatric Surgery	Professor	Jun Fujishiro
Department of Aging Science	Professor	Masahiro Akishita
<b>Surgical Sciences</b>		
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
<b>Health Sciences and Nursing</b>		
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
Department of Clinical Nursing	Professor	Noriko Yamamoto
	Professor	Megumi Haruna
	Professor	Norito Kawakami
	Professor	Hiroshi Sanada
<b>International Health</b>		
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
<b>School of Public Health</b>		
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
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
Clinical Trial Data Management		
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 Life Support Technology (Molten)	Project Professor	Taketoshi Mori
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 Preventive Medicine for Locomotive Organ Disorders	Project Professor	Noriko Yoshimura
Laboratory for New Generation Drug Discovery	Project Associate Professor	Hideaki Ando
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 Fujii

### 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
Bariatric & Metabolic Care	Project Associate professor	Susumu Aiko
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 Professor	Takashi Kadowaki
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

### 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	Hirofumi Nakatomi
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	Akira Oka
Pediatric Surgery	Head	Jun Fujishiro
Obstetrics and Gynecology	Head	Tomoyuki Fujii
Neuropsychiatry	Head	Kiyoto Kasai
Radiology	Head	Osamu Abe
Acute Medicine	Head	Naoto Morimura
<b>Central Clinical Facilities</b>		
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	Tomoyuki Fujii
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
Organ Transplantation Service	Head	Kiyoshi Hasegawa
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	Akira Oka
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	Takeshi Iwatsubo
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 and Anatomy

## Associate Professor

Yoshimitsu Kanai, M. D.

## Lecturer

Yosuke Tanaka, M. D.

## Research Associate

Tadayuki Ogawa, Ph. D.

**Home page** <http://cb.m.u-tokyo.ac.jp/>

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## 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, immunocytochemistry, molecular biology, molecular genetics such as gene targeting and transgenic mouse approaches, molecular biophysics and structure biology including X ray crystallography and cryoelectron microscopy.

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

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

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

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

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

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5. Iwata S., Morikawa M., Takei, Y., and N. **Hirokawa**. An activity-dependent local transport regulation via degradation and synthesis of KIF17 underlying cognitive flexibility. *Science Advances* 2020 6: eabc8355

# 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>

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## 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), Motohiro Morikawa, Yuta Komori, and Shuohang Gao (MSTP students), Akiko Oosakaya, Ayako Ogasawara, Koshi Chiba (technical assistant), Kazuhiro Nakamura (Advanced Academic Specialist), and Mikako Yanagiuchi and Aiko Shibata (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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5. R. Danev, H. Yanagisawa, and M. Kikkawa. Cryo-Electron Microscopy Methodology: Current Aspects and Future Directions. *Trends Biochem Sci*, 44(10):837–848, 2019.
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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., Shinichiro Tsutsumi, M.D., Ph.D.

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

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## 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 28 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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6. Kashiwagi, Y., Higashi, T., Obashi, K., Sato, Y., Komiyama, N., Grant, S. G. N. and **S. Okabe** Computational geometry analysis of dendritic spines by structured illumination microscopy *Nature Communications* 2019 10, 1285. doi: 10.1038/s41467-019-09337-0.
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12. International Brain Initiative: An innovative framework for coordinated global brain research efforts. International Brain Initiative (J. Bjaalie and **S. Okabe** corresponding authors) *Neuron* 2020 105(2):212-216. doi: 10.1016/j.neuron.2020.01.002.
13. Tanaka S, Masuda Y, Harada A, **Okabe S**. Impaired actin dynamics and suppression of Shank2-mediated spine enlargement in cortactin knockout mice. *Microscopy (Oxf)*. 2020 Mar 9; 69(1):44-52. doi: 10.1093/jmicro/dfaa001.
14. **Okabe, S.** Recent advances in computational methods for measurement of dendritic spines imaged by light microscopy. *Microscopy (Oxf)*. 2020 Jul 30;69(4):196-213. doi: 10.1093/jmicro/dfaa016.

# **Molecular Cell Biology**

## **2. Biochemistry and Molecular Biology**



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# Department of Molecular Biology

## Professor

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

## Lecturer

Hayashi Yamamoto, Ph.D.

## Research Associate

Hideaki Morishita, M.D., Ph.D. (~Aug 2019), 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., Roland Knorr, Ph.D. (~Jan 2019), Tomoya Eguchi, M.D., Ph.D.

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

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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 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 2018, we reported the following novel findings.

Autophagosome formation requires the covalent attachment of the ubiquitin-like protein ATG12 to ATG5. However, why both proteins need to be covalently bound has been unclear for two decades. Unexpectedly, we found that the Apicomplexan parasites *Plasmodium* and *Toxoplasma* and the yeast *Komagataella phaffii* (former *Pichia pastoris*) do not possess the enzyme required for covalent binding of ATG12 and ATG5, and that ATG12 and ATG5 exist as a stable, functional, non-covalent complex. That is, ATG12 and ATG5 do not necessarily have to form a covalent complex, and the ATG12 system in some organisms may have evolved to a simpler, non-covalent version (Pang et al. *Nat Struct Mol Biol* 2019).

Autophagy degrades intracellular components

not only nonselectively but also selectively. In the search for novel molecules selectively degraded by autophagy, we identified TEX264. TEX264 is present on the endoplasmic reticulum membrane and binds to autophagosome LC3 at the carboxy terminus. In cells lacking TEX264, the degradation of endoplasmic reticulum by autophagy (called ER-phagy) was remarkably suppressed. Thus, TEX264 functions as a novel ER-phagy adaptor (Chino et al. *Mol Cell* 2019).

## 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.

Some of the autophagy-related factors have also been found to have functions other than autophagy. For example, using zebrafish and mice, we found that the ER membrane protein VMP1 is required not only for autophagy but also for the process of lipoprotein detachment from the ER to the lumen. Since autophagy, lipoprotein secretion, and lipid droplet formation involves dynamic morphological changes of the ER, VMP1 may play a role in the homeostasis and remodeling of the ER membrane. Recently, an association between single nucleotide polymorphisms (SNPs) in the human *VMP1* gene and blood cholesterol levels has been reported. Our results would provide new insights into the mechanism of lipoprotein formation and secretion and contribute to the understanding of relevant diseases.

## 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-LC3 $\Delta$ G, 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

## Professor

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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 the members of the the Laboratory of Microenvironmental and Metabolic Health Sciences.

## Research activities

The main theme of this research project is to clarify the role of lipids in health and diseases. Lipids represent the largest source of energy in living organisms, are main components constituting cell membranes, and also act as signal molecules. Lipids are environmental nutritional factors ingested from foods, as well as tissue microenvironmental regulators that spatiotemporally coordinate biological responses after being metabolized to specific bioactive lipids. By performing comprehensive lipid analysis (lipidomics) on gene-manipulated mice for lipid-metabolizing enzymes, particularly those in the phospholipase A<sub>2</sub> (PLA<sub>2</sub>) 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

Polyunsaturated fatty acids (PUFAs) confer health benefits by preventing inflammation and obesity and by increasing thermogenesis in brown and beige adipocytes. As well as being supplied exogenously as nutrients, PUFAs are largely stored in membrane glycerophospholipids and released by phospholipase A<sub>2</sub>s (PLA<sub>2</sub>s). However, the molecular identity of the PLA<sub>2</sub> subtype(s) that supplies endogenous PUFAs for metabolic homeostasis remains unclear. PLA2G2D, a secreted phospholipase A<sub>2</sub> (sPLA<sub>2</sub>) isoform, is constitutively expressed in M2 macrophages in white adipose tissue (WAT) and shows a reciprocal correlation with obesity. Studies using global and macrophage-specific *Pla2g2d*<sup>-/-</sup> mice have revealed that PLA2G2D ameliorates diet-induced obesity and insulin resistance and counteracts the proinflammatory M1 macrophage bias in WAT. Moreover, PLA2G2D increases energy expenditure and thermogenesis by facilitating WAT browning. Mechanistically, PLA2G2D constitutively supplies a pool of PUFAs, ω3 in particular, in WAT. These results underscore the contribution of the M2 macrophage-driven PLA2G2D-PUFA axis to metabolic health (Sato et al, *Cell Reports* 2020).

Choline supplies methyl groups for regeneration of methionine and the universal methyl donor *S*-adenosylmethionine (SAM) in the liver. Although phosphatidylcholine (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 conversion of

lysophosphatidylcholine 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, and reduced fat mass with adipocyte browning. Accordingly, mutant mice are lean, display growth retardation, and die prematurely. Thus, the methyl group flux from choline endogenously generated through PC breakdown by the PNPLA7 axis is crucial for liver functions and energy homeostasis (manuscript in preparation).

## 2) Cardiovascular diseases

Aortic dissection is a life-threatening aortopathy involving separation of the aortic wall, yet the underlying mechanisms are still incompletely understood. Epidemiological evidence suggests the beneficial effects of unsaturated fatty acids on cardiovascular health. Here we show that PLA2G5, a sPLA<sub>2</sub> isoform expressed in aortic endothelial cells, plays a protective role against aortic dissection by endogenously mobilizing vasoprotective lipids. Global and endothelial cell-specific *Pla2g5*-deficient mice frequently develop aortic dissection shortly after infusion of angiotensin II (AT-II). In the AT-II-treated aorta, endothelial PLA2G5 mobilizes oleic and linoleic acids, which attenuate ER stress, increase the expression of lysyl oxidase, and thereby stabilize the extracellular matrix in the aorta. The increased susceptibility of *Pla2g5*<sup>-/-</sup> mice to aortic dissection was rescued by dietary supplementation with oleic or linoleic acid. These findings reveal an unexplored functional link between sPLA<sub>2</sub>-driven phospholipid metabolism and aortic stability, possibly contributing to the development of novel diagnostic and/or therapeutic strategies for aortic dissection (Watanabe et al, *J Biol Chem* 2020; selected as an Editors' Pick).

## 3) Skin diseases

Lipids play crucial roles in skin homeostasis and diseases. We have currently reported that PLA2G2F, an epidermal sPLA<sub>2</sub>, 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 iPLA<sub>2</sub> family whose mutations cause autosomal recessive congenital

ichthyosis, acts as a transacylase to produce  $\omega$ -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 PLA<sub>2</sub> knockout strains, as well as by gene expression profiling of PLA<sub>2</sub>-related genes in mouse and human skins, we have identified several PLA<sub>2</sub>s that appear to be linked to skin diseases. Of these, we found that PLA2G4E (cPLA<sub>2</sub> $\epsilon$ ), 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 lipid mediator *N*-acylethanolamine (NAE) that has an anti-inflammatory function. *Pla2g4e* deficiency lead to 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. This is the first demonstration of the role of PLA2G4E as an *N*-acyltransferase *in vivo* (manuscript in preparation).

## 4) Allergic diseases

We have currently shown that PLA2G3, an sPLA<sub>2</sub> isoform secreted from mast cells, promotes mast cell maturation by driving the paracrine PGD<sub>2</sub> circuit in cooperation with microenvironmental fibroblasts (Taketomi et al, *Nat Immunol* 2013) and that PAF-AH2, a unique PLA<sub>2</sub> that hydrolyzes oxidized phospholipids, ensures optimal mast cell activation and thereby allergic responses through producing unique EPA/DHA metabolites ( $\omega$ 3 epoxides) (Shimanaka et al, *Nat Med* 2017). We are now analyzing other PLA<sub>2</sub> knockout strains that have alterations in allergic responses.

## 5) Neuronal diseases

Mutations in the *PLA2G6* gene, which encodes PLA2G6 or iPLA<sub>2</sub> $\beta$ , are responsible for *PARK14*-linked Parkinson's disease with  $\alpha$ -synucleinopathy. However, it is unclear how *PLA2G6* mutations lead to dopaminergic (DA) neurodegeneration in association with  $\alpha$ -synuclein ( $\alpha$ -Syn) aggregation. We found that *PLA2G6*-deficient *Drosophila* exhibits degeneration of DA neurons, with defective neurotransmission and motor ability. Lipidomics analysis of the brain reveals that the acyl-chain length of phospholipids is

shortened by *PLA2G6* loss, which causes membrane lipid disequilibrium-induced ER stress. Introduction of native human *PLA2G6* or C19orf12, an orphan protein residing in the mitochondria-ER contact site, in *PLA2G6*-deficient flies rescues the phenotypes associated with altered lipid composition, ER stress and DA neurodegeneration, whereas that of a disease-associated missense mutant, *PLA2G6* A80T, fails to suppress these phenotypes. The acceleration of  $\alpha$ -Syn aggregation by *PLA2G6* deficiency or A80T expression is suppressed by the administration of linoleic acid, which corrects lipid composition in the fly brain. These results suggest that membrane remodeling by *PLA2G6* is required for the survival of DA neurons and  $\alpha$ -Syn stability (Mori et al, *PNAS* 2019).

## 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 guidances 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).

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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, 2 postdoctoral fellow, 7 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 craniofacial 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 verified that *Hoxa2*, a member of the Hox gene clusters, is sufficient for endowing Hox-free pharyngeal arch tissues with the second pharyngeal arch identity by introducing ectopic *Hoxa2* expression. *Hoxa2* gene manipulation also identified the dorso-ventral boundary in the pharyngeal region, together with experiments using mice carrying mutations in ET-1/ETAR and its downstream genes *Dlx5* and *Dlx6*.

## (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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# Department of Advanced Structural Studies

## Professor

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## Introduction and Organization

Our laboratory was established in November 2018 as part of an initiative to strengthen the molecular structural biology research at the Graduate School of Medicine. 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 Isao Takahashi (technical assistant).

## 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. We also gave 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

## Research activities

Our research is aimed at elucidating the structure-function relationships of proteins and

cellular components. We hope to contribute to the general knowledge of the molecular mechanisms behind chronic diseases and thereby to help develop effective treatments.

Currently, we are investigating an important class of membrane proteins called G protein-coupled receptors (GPCRs). GPCRs constitute the largest protein superfamily in the human genome and are implicated in numerous illnesses, such as diabetes, obesity, nervous system disorders, asthma, allergies, cardiovascular disorders, cancer, and others. As such, they also represent the biggest group of drug targets and are the subject of approximately 30% of approved drugs. For our structural investigations, we employ the presently flourishing method of cryo-EM single particle analysis to determine the atomic structure of GPCRs in complex with both native and synthetic ligands. We have an ongoing international collaboration with a group from Monash University in Australia that specializes in GPCR pharmacology and has substantial experience in expression and purification of target complexes. In the past year, our results comprise more than twenty sub-3 Å full-length unmodified GPCR structures, one third of which are at resolutions better than 2.5 Å. This is an unprecedented achievement both in terms of resolution and throughput. To reach such level of success, we conducted a thorough optimization of the experimental parameters for both sample preparation and cryo-EM data collection. We implemented a highly efficient “tandem” approach that combined methodology testing with actual data collection and therefore did not require extra usage time on the costly

and heavily booked electron microscope equipment. The exceptional results from our group and all other groups that utilize the state-of-the-art equipment at the cryo-EM facility showcase both the accelerating evolution of cryo-EM as a technique and the very successful launch of the new cryo-EM facility at the Graduate School of Medicine.

Despite the exponential growth of the field in recent years, there are still many areas where further advances are possible and/or are highly desirable. In addition to our structural studies, we are also working on the development of new experimental methods for cryo-EM. One of the 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. Other directions of our research include improvement of the throughput and performance of electron cryo-tomography and cryo-EM experiment automation. In the future, we plan to expand our investigations towards state-of-the-art deep learning experiment augmentation and improved data processing algorithms.

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# **Functional Biology**

## **1. Physiology**

# Department of Integrative 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<sup>2+</sup>) 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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「神経 - グリア - fMRI 信号を繋ぐ脳活動イメージング」, 実験医学増刊号「グリア」(松井広, 田中謙二編) (羊土社), 2019年10月(和文)

# Department of Cellular and Molecular Physiology

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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, 5 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) Arm movements induced by non-invasive optogenetic stimulation of the motor cortex in the common marmoset

Which brain area drives hand/arm movements after learning or brain injury? When does motor cortical activity generate appropriate hand/arm movements? To address these issues, it is necessary to manipulate motor cortical activity in a controlled manner.



Optogenetics has been applied to manipulate the neuronal activity related to a variety of brain functions in non-human primates and rodents. With regard to the motor control system of non-human primates, saccadic eye movements were modulated by optogenetic activation and/or inactivation of cerebral cortical neurons. However, optogenetic stimulation failed to induce or modulate any limb movements in non-human primates. This is in contrast to mice, in which Channelrhodopsin-2 (ChR2) stimulation of layer 5 neurons in multiple subregions of the motor cortex successfully induced different types of complex forelimb movements. This may be because the number of photoactivated neurons in the non-human primate did not reach a level sufficient to elicit hand/arm movements, and/or because the activation patterns of neurons and/or the types of activated neurons differ between optogenetic and electrical stimulation.

We used the common marmoset (*Callithrix jacchus*) to overcome these possible problems, as this New World monkey has a smaller motor cortex than macaque and squirrel monkeys. We therefore expected it to be easier to photostimulate a relatively larger proportion of the motor cortical neurons dominating the hand/arm movements. To do this, we used adeno-associated viruses (AAVs) with a tetracycline-inducible gene expression system that amplifies neuronal expression of induced genes. We previously used this system carrying the GCaMP gene to establish two-photon calcium imaging of cortical neurons in anesthetized and behaving marmosets. We also used a ChR2 variant (E123T/T159C) with fast kinetics that was able to follow each high-frequency photostimulation, as is commonly used in electrical stimulation (100–350 Hz). Furthermore, we used a cranial window to permit stimulation of a larger area (diameter of 1–2 mm) than is possible with an optical fiber inserted into the cortex.

In an awake state, forelimb movements could be induced when channelrhodopsin-2-expressing neurons in the motor cortex were illuminated by blue laser light with a spot diameter of 1 or 2 mm through a cranial window without cortical invasion. Forelimb muscles responded 10–50 ms after photostimulation onset. Long-duration (500 ms) photostimulation induced discrete forelimb movements that could be markerlessly tracked with CCD cameras and a

deep-learning algorithm. Long-duration photostimulation mapping revealed that the primary motor cortex is divided into multiple domains that can induce hand and elbow movements in different directions.

In the visually cued pole-pull task, weak 500 ms photostimulation, which did not induce visible forelimb movements at rest, at any time point in respect to the cue onset caused the pole to be slightly moved in the same direction as the movement induced by the strong 500 ms stimulation. This suggests that M1 neurons are more activated by and more sensitive to photostimulation during a voluntary movement task, than they are at rest. In two marmosets, the photostimulation that started 1500 ms before the cue onset did not affect the reward reaching time, suggesting that the preceding perturbation of the M1 activity can be amended for ~1 s before the onset of the voluntary movement. By contrast, when the photostimulation started at the cue onset for one marmoset, and 500 ms before the onset for another marmoset, the reward reaching time changed according to the direction of the induced movement. The difference in the effect of the time window between the two marmosets might be due to the difference in the extent of the photoactivation and/or stimulation position. These results suggest that the voluntary movement was biased toward the movement dominated by the domain of M1 with high activity. Combined with calcium imaging, all-optical interrogation of motor circuits should be possible in behaving marmosets.

(2) Neural dynamics in the mouse secondary and primary motor cortices during self-initiated and externally triggered movements

Voluntary movements can be either self-initiated or externally triggered. The higher motor cortex (M2) in primates is activated differently in these scenarios. However, little is known about whether the presence or absence of an external cue primarily determines which type of M2 neural activity is evoked when the same movement is executed in both contexts. To address this, we improved on previously developed mouse forelimb movement tasks. We trained head-fixed mice to perform a self-initiated lever-pull task (SI) and an external cue-triggered lever-pull task (ET). Blocks of these tasks (SI and ET blocks) were

switched several times within one session. During task performance, we conducted concurrent calcium imaging of layer 2/3 neurons in M2 and M1 using a super-wide-field two-photon microscope (Terada et al., 2018). As expected, the proportion of neurons that exhibited movement-related activity specific to either block was larger in M2 than in M1. Neural population analysis showed that M2 population activity around the onset of lever pull was markedly different between the SI and ET blocks; this could not be explained by slight differences in body movement, including forelimb and orofacial movements, between the blocks. By contrast, the difference in M1 population activity was smaller than that in M2 population activity and well explained by the behavioral differences. In a majority of trials, M2 population activity showed the post-switch block type immediately after the block switch. However, in some trials, M2 population activity showed the pre-switch block type. In addition, during approximately half of the lever pulls that occurred mistakenly at the interval between the external cues in the ET block, the M2 population exhibited ET block-type activity. These results indicate that the type of M2 population activity evoked depends on both the present and preceding contexts. Both types of M2 population activity presumably evoke the inseparable M1 ensemble whose activity varies to the same extent that the body movement varies.

(From abstract in Neuroscience 2019)

(3) Value information that affects decision making is transmitted from the thalamus to the motor cortex

We can estimate the values of presented cues and decide whether to act after each cue presentation through operant conditioning. It is thought that the striatum is a critical region to estimate such cue values and that the motor cortex generates the motor command for the appropriate action. However, it is unknown whether and how cue value information estimated in the striatum is transmitted to the motor cortex, including the secondary and primary motor cortical areas (M2 and M1). Anatomically, the motor thalamus receives the projection descending from the striatum and sends axons to M2 and M1. We recently reported movement-related activity in thalamocortical (TC) axons projecting from the motor thalamus to M1

in mice performing a self-initiated lever-pull task (Tanaka et al., 2018). Here, we developed a new reward-based lever-pull task. In this task, one of two cues with different sound frequencies (cues A and B) was randomly presented in each trial. After a cue period, the mice chose whether to pull the lever with their right forelimb. When the mice pulled the lever, a water reward was delivered at a high probability in the cue A trial and a low probability in the cue B trial. After training for this task, the mice pulled the lever more frequently in the cue A trial than in the cue B trial. During the task, we conducted two-photon calcium imaging of TC axons in the left M2 and M1. Activity of a subset of TC axonal boutons increased after cue A onset, while few boutons exhibited increased activity after cue B onset. Linear discriminant analysis revealed that the emergence of cue information transmitted by M2-projecting TC axonal boutons preceded that of cue information transmitted by M1-projecting ones. Channelrhodopsin-2 stimulation of M2-projecting TC axons during the cue period increased the frequency with which the mice pulled the lever in the cue B trial. These results suggest that M2-projecting axons of the motor thalamus transmit cue value information that can affect subsequent decision making.

(From abstract in Neuroscience 2019)

(4) Development of a behavioral paradigm and a model-based analysis with reinforcement learning

Animals choose something and act appropriately in their daily life. They get something good and bad at the same time through their choice. The former is the reward such as food and water and the latter is the cost and/or energy that inevitably accompany body movements. Animals have to compute both of them before they decide whether they act or not. However, it is poorly understood how the rewards obtained by animals' action and the costs accompanying their action affect their decision-making and whether doing nothing is actively chosen or not.

To address these issues, we developed a simple behavioral task focusing on water reward and physical effort (forelimb movement) and performed a model-based analysis with reinforcement learning, a framework using animal behavior and the outcomes. In our task, mice were let to choose whether to pull

the lever or not in response to two different tones associated with two different probabilities of water delivery (reward probabilities) following a successful lever pull. No reward was delivered after either tone when the lever was not successfully pulled. After two-week training sessions, most of the mice frequently pulled the lever after tones with higher reward probability but infrequently did after tones with lower one. This tendency was similarly observed when different sets of reward probabilities were used. We then fit the changes in their behavior during the training sessions by several models with different free-parameter sets. In terms of the physical effort, we assumed two cases: “cost model” and “saving-energy model”. “Cost model” is that the mice get the cost (negative reward) when they choose ‘to pull’ because they should get tired. “Saving-energy model” is that they get ‘rewarded’ when they choose ‘not to pull’ because the mice could save the physical effort. We compared these models with the use of Bayesian information criterion and found that “saving-energy model” described their learning process better than “cost model”.

These results suggested that the mice found something good in the choice of ‘not to pull’ even though they got no water reward. The mice might regard avoiding the costs as ‘reward’, and they might actively choose ‘not to pull’ rather than they just didn’t choose ‘to pull’. This paradigm will help us to understand the active choice of ‘doing nothing’ and how animals evaluate the cost or energy.

(From abstract in the 43rd Annual Meeting of the Japan Neuroscience Meeting)

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# Department of Neurophysiology

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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), 4 postdoctoral fellows, 10 graduate students, 4 research student and 5 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 gastricnemius 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. Moreover, for mutual communication between the laboratories with similar interests in neuroscience, we have a weekly joint seminar with Department of Cellular Neurobiology, Division of Structural Physiology, Department of Cellular and Molecular Physiology, Department of Integrative Physiology, and Division of Animal Resources.

## **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 ap-

proaches including electrophysiology, pharmacology, morphology, and genetic engineering of mouse. We particularly focus on observing neuronal activities in real time in intact neurons. We use whole-cell patch clamp recording, calcium imaging, two-photon imaging and their combinations in various preparations (cultured neurons, brain slices and intact animals) and investigate molecular mechanisms of synaptic transmission and plasticity.

The main subjects of our research are as follows

(1) Refinement of synaptic organization during cerebellar development:

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

(2) Retrograde synaptic modulation mediated by endogenous cannabinoids:

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

(3) Synaptic integration in intact animals:

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

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# **Functional Biology**

## **2. Pharmacology**

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# Department of Cellular and Molecular Pharmacology

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## Introduction and Organization

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

## Teaching activities

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

## Research activities

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

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

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

### 2) Study of the mechanism underlying the exocytosis of neurotransmitter

For understanding of regulation mechanism underlying neuronal circuit in mammalian central nervous system, elucidation of the neurotransmitter release machinery is indispensable. Aiming at imaging neurotransmitter glutamate, we developed a novel optical glutamate probe by our high-throughput screening system as described above. Using this probe, we successfully visualized presynaptically released glutamate with a single synapse resolution in cultured hippocampal neurons. We quantitatively analyzed released glutamate at individual synapses and revealed

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

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

Recently, nanoscale molecular distribution in synapses is suggested to be a key determinant of synaptic function. To reveal the relationship between the 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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# Department of Systems Pharmacology

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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 six 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

With our members from different backgrounds, we would like to realize experimental systems biology at the organism level, 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. Additionally, we execute a comprehensive study to examine dynamic properties of the biological system inside cell-to-tissue scale, and their relations to organism-level phenotypes.

### 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 (Ukai et al. Nat Protoc. 2017; Sumiyama et al. PLOS ONE 2019). Using these methods, we successfully generated knockout mice for acetylcholine muscarinic receptors and leak potassium channels and analyzed these sleep phenotypes in the first generation (Niwa et al., Cell Rep. 2018; Yoshida et al., PNAS 2018).

### 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 imaging at single-cell resolution (represented by Susaki et al., Cell, 2014; Tainaka et al., Cell Rep. 2018). Among our concerted efforts to expand CUBIC technology, we recently applied the tissue clearing and 3D imaging to organs other than the brain (e.g., Hasegawa et al., Kidney Int. 2019), whole mouse body (e.g., Tainaka et al. Cell 2014; Kubota et al. Cell Rep. 2017), and human pathological specimens (e.g., Nojima et al. Sci Rep. 2017). By integrating the swelling-based clearing protocol (CUBIC-X) and high-throughput and high-resolution light-sheet microscopy (MOVIE), we also succeeded in generating a single-cell resolution whole mouse brain atlas (CUBIC-Atlas) (Murakami et al. Nature Neurosci 2018; Murakami et al., Nat Protoc. 2019). Furthermore, we have challenged developing a versatile and efficient three-dimensional histopathological method (CUBIC-HistoVIsion) (Susaki et al., Nat Commun. 2020).

Because of its rapid imaging capability of the whole organ/body, CUBIC offers extraordinary novel discoveries in life science and medical research. Together with several major laboratories involving tissue-clearing development, we introduced the latest circumstances regarding the clearing-imaging technology (Ueda et al., Nat Rev Neurosci. 2020; Ueda et al., Neuron 2020).

### 3) Mechanism of dynamic homeostasis in sleep/wake cycle

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  $\text{Ca}^{2+}$ -dependent neuronal hyperpolarization pathway affects sleep duration in mammals (Sunagawa et al., Cell Reports 2016; Tatsuki et al., Neuron 2016; Ode and Ueda. Cold Spring Harb. Perspect. Biol. 2018; Shi and Ueda. BioEssays 2018; 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. They also indicated that REM sleep is not critical for the survival of animals.

Given our numerous studies of sleep, circadian rhythms, and related technologies, our findings will contribute to our understanding of these diseases, including psychiatric and neurodegenerative disorders. We have proposed perspectives on human circadian rhythms, sleep, and genetics for future research (Ode and Ueda, Cold Spring Harb. Perspect. Biol. 2018; Ode and Ueda, Mol. Syst. Biol. 2018; Ukai et al., Current Opinion in Biotechnology 2019; Millius et al., F1000Res. 2019) and are currently expanding our approach to human sleep phenotyping.

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# **Pathology, Immunology and Microbiology**

## **1. Pathology**

# Department of Pathology and Diagnostic Pathology

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Kei Sakuma, Kimiko Takeshita, M.T.

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## Introduction and Organization

Department of Pathology and Diagnostic Pathology is responsible for the practice of diagnostic pathology, education, and research in cooperation with 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”.

After retirement of former Professor, Prof. Fukayama, Dr. Tetsuo Ushiku was appointed to a professorship at the Department of Pathology and Diagnostic Pathology of the University of Tokyo on May 1<sup>st</sup>, 2019. Dr. Misumi moved to National Center for Global Health and Medicine. Dr. Miyama become an associate of the department and Dr. Rokutan became an associate of the University of Tokyo Hospital.

Two postgraduate students (Hakozaki and

Furuhata) finished the course and received Ph.D. In the new fiscal year, 2020, six new students (5 in the doctoral course and one in the master's course) will enter the postgraduate course, and there will be 24 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 1<sup>st</sup> grade medical students in collaboration with Department of Molecular Pathology, Systemic Pathology for the 2<sup>nd</sup> grade, Elective Clinical Clerkship for the 4<sup>th</sup> grade, and Clinical Clerkship for the 3<sup>rd</sup>/4<sup>th</sup> 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.

We registered substantial cases of whole slide images (WSI) in the research project of Japanese Society of Pathology "Database of Pathology-WSI for Development of Artificial Intelligence (AI) Technique and AI-based Support System for Pathology Diagnosis" in 2017. We also examined the problems in image registration in the hospital with the Departments of Radiology and Neurosurgery.

## Teaching activities

We provide General Pathology Course for the 1<sup>st</sup> 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. Handouts are available in every half course of the pathologic exercises, and all slides used in the course are accessible on our website as virtual slides (digital images of the slides).

In Clinical Clerkship for all 3<sup>rd</sup>/4<sup>th</sup> 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 in-house as well as other hospitals.

Both Clinical Clerkship course (4<sup>th</sup> grade) and Free Quarter program (1<sup>st</sup>/2<sup>nd</sup> 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. One of our research developments was obtained from genomic analysis of early-stage gastric cancer done by Dr. Rokutan, which demonstrated the mutation status in *APC* and *TP53* is diagnostically useful in differentiating malignant from benign (ref 17). We also expand our research to cover pathologically diverse gastric cancer.

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 tumors (Drs. Shinozaki-Ushiku, Abe and Hinata), pancreatobiliary tumors (Drs. Tanaka and Yamauchi, ref 19), bone and soft tissue tumors (Dr. Makise), and urinary tract tumors (Dr. Miyama). We also collaborate with other laboratories in and outside the University to develop new technologies such as AI (Drs. Abe and Hinata), tissue clearing technique, and tissue processing robots in pathology practice.

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# Department of Molecular Pathology

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## Introduction and organization

Our department has a more than 100-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 2020, 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. 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 20 years.

Some of our graduate students had been supported by the GPLLI Graduate Program for Leaders in Life Innovation at the University of Tokyo from the Ministry of Education, Culture, Sports, Science and Technology, Japan (MEXT). From 2018, World-leading INnovative Graduate School Program for Life Science and Technology (WINGS-LST) has started. These programs will stimulate interaction between students and scientists in the programs as well as those from other laboratories ([square.umin.ac.jp/gplli/](http://square.umin.ac.jp/gplli/); [square.umin.ac.jp/wings-lf/](http://square.umin.ac.jp/wings-lf/)).

## Research activities

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

From 2015, our research is mainly supported by a Grant-in-Aid for Scientific Research (S) on

“Transcriptional regulation by TGF- $\beta$  signaling and its relation to progression of cancer” (15H05774) from the Japanese Society for the Promotion of Science (JSPS). From 2017, our research is also supported by a Grant-in-Aid for Scientific Research on Innovative Area on Integrated Analysis and Regulation of Cellular Diversity (17H06326) from MEXT.

Followings are some research results obtained at our laboratory in 2019.

1) *Roles of the BMPRII/ALK-1/SMAD/ATOH8 axis in the development of pulmonary arterial hypertension*

Perturbations of bone morphogenetic protein (BMP) signaling in endothelial cells are involved in vascular diseases, such as pulmonary arterial hypertension (PAH). We demonstrated that the transcription factor ATOH8 is a direct target of BMP signaling factors Smad1/5, and it is induced in a BMP-dependent manner. In zebrafish and mice, gene silencing of *Atoh8* failed to cause an arteriovenous malformation (AVM)-like phenotype, which is observed by mutations in *Alk1* gene. In contrast, *Atoh8*-knockout mice showed a PAH-like phenotype, such as increased pulmonary arterial pressure and right ventricular hypertrophy. Furthermore, expression levels of ATOH8 were decreased in the lungs of PAH patients. We revealed that ATOH8 physically associates with hypoxia-inducible factor 2 $\alpha$  (HIF-2 $\alpha$ ) and decreases its expression levels in cultured cells, leading to attenuation of the induction of HIF-2 $\alpha$  target genes in response to hypoxia. These findings suggest that the BMP receptor type II/ALK-1/SMAD/ATOH8 axis may attenuate hypoxic responses in endothelial cells in the pulmonary circulation and may play an important role in prevention of the development of PAH (Morikawa et al. *Sci Signal* 2019).

2) *Tyrosine kinase EPHA6 sensitizes glioma-initiating cells towards BMP-induced apoptosis*

BMP signaling plays critical roles in the development of glioblastoma multiforme (GBM). BMP suppresses tumorigenicity of GBM cells through induction of differentiation and apoptosis of glioma-initiating cells (GICs). However, BMP fails to induce tumor suppressive effects on some GICs. By a phosphoreceptor tyrosine kinase array analysis, we found that phosphorylation of EPHA6 (erythropoietin-producing hepatocellular carcinoma receptor A6) was regulated

by BMP-2 in some GICs. Analysis of The Cancer Genome Atlas (TCGA) dataset revealed that expression levels of EPHA6 were lower in patients with GBM than those in the normal brain; moreover, high EPHA6 expression was correlated with better prognosis. Ectopic expression of EPHA6 increased the susceptibility of GICs to apoptosis induced by BMP-2. The cooperative effect on apoptosis induction by EPHA6 and BMP signaling depended on the kinase activity of BMP type I receptor, but not on the kinase activity EPHA6. Overexpression of EPHA6 in GICs induced the formation of a protein complex of EPHA6 and the BMP type I receptor ALK-2, which was correlated with BMP-induced apoptosis in GICs. Intracranial injection of GICs into immunodeficient mice demonstrated that gain-of-function of EPHA6 together with BMP-2 pretreatment attenuated the tumor progression of GBM in the mouse brain and prolonged the mouse survival. Thus, EPHA6 together with BMP signaling leads to apoptotic cell death in GICs, and thus possibly functions as a tumor suppressor in GBM (Raja et al. *Cancer Sci* 2019).

3) *FGF signals regulate TGF- $\beta$ -induced endothelial-myofibroblast transition of tumor endothelial cells*

Tumor microenvironment contains various components, including cancer cells, blood and lymphatic vessels, and cancer-associated fibroblasts (CAFs). CAFs are comprised of tumor-promoting myofibroblasts and tumor-suppressing fibroblasts. TGF- $\beta$  is known to induce the formation of myofibroblasts and other types of mesenchymal (non-myofibroblastic) cells from vascular endothelial cells. Recent reports showed that fibroblast growth factor 2 (FGF2) regulates TGF- $\beta$ -induced endothelial- mesenchymal transition (EndMT), but the mechanisms that control transcriptional networks for the formation of distinct groups of fibroblasts remain unclear. We investigated the roles of FGF2 in the regulation of TGF- $\beta$ -induced EndMT of tumor endothelial cells (TECs). We showed that FGF signals in TECs inhibit TGF- $\beta$ -induced endothelial- myofibroblast transition (End-MyoT), leading to suppressed formation of contractile myofibroblast cells. However, FGF signals can also collaborate with TGF- $\beta$  in promoting the formation of active fibroblastic cells with migratory and proliferative properties. FGF2 modulated formation of myofibroblastic and non-myofibroblastic cells by

TGF- $\beta$  from TECs through transcriptional regulation of various mesenchymal markers and growth factors. Moreover, TECs treated with TGF- $\beta$  were more competent in promoting *in vivo* tumor growth compared to TECs treated with TGF- $\beta$  and FGF2. We further showed that Elk1 regulated FGF2-induced inhibition of End-MyoT through inhibition of TGF- $\beta$ -induced transcriptional activation of the  $\alpha$ -smooth muscle actin promoter by myocardin-related transcription factor-A. These findings suggest that TGF- $\beta$  and FGF2 oppose and cooperate with each other during the formation of myofibroblastic and non-myofibroblastic cells from TECs, and these functions of TGF- $\beta$  and FGF2 determine the characteristics of mesenchymal cells in the tumor microenvironment (Akatsu et al. Mol Oncol 2019).

#### 4) Comparative analysis of TTF-1-binding DNA regions in SCLC and non-SCLC

Thyroid transcription factor-1 (TTF-1, encoded by the NKX2-1 gene) is highly expressed in both small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC). TTF-1 antagonizes the effect of TGF- $\beta$  in the induction of epithelial-mesenchymal transition (EMT) in NSCLC. However, it still remains to be elucidated how the functional roles of TTF-1 differ between SCLC and NSCLC. We compared the genome-wide distributions of TTF-1 binding regions and the transcriptional programs regulated by TTF-1 using a human SCLC cell line NCI-H209 (H209), and a human lung adenocarcinoma (NSCLC) cell line NCI-H441 (H441), by ChIP-seq (chromatin immunoprecipitation-sequencing) and RNA-seq (RNA-sequencing) analyses. TTF-1 binding regions in H209 and H441 cells differed by 75.0% and E-box motifs were highly enriched in the TTF-1 binding regions of H209 SCLC cells. Transcriptome profiling showed that TTF-1 is involved in neuroendocrine differentiation in H209 SCLC cells. ASCL1 (also known as ASH1) is an E-box binding basic helix-loop-helix transcription factor, and a lineage-survival oncogene of SCLC. We found that TTF-1 and ASCL1 were coexpressed and bound to adjacent sites on target genes in SCLC, and cooperatively regulate transcription of them. Moreover, TTF-1 regulated expression of the Bcl-2 apoptosis-related gene family and showed anti-apoptotic function in SCLC. These findings suggest that TTF-1 promotes SCLC growth and

contributes to neuroendocrine and anti-apoptotic gene expression by partly coordinating with ASCL1 (Hokari et al. Mol Oncol 2019).

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# **Pathology, Immunology and Microbiology**

## **2. Microbiology**

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# Department of 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 21 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), 9 graduate school students (Mr. and Ms. Knight, Wada, Imai, Tahmina, Marrero, Wu, Wu, Hikawa, Yau), and 3 research students (Ms. 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. High-molecular-weight hyaluronan is a Hippo pathway ligand that directs cell density-dependent growth inhibition via PAR1b

The tumor-suppressive Hippo signaling pathway plays a key role in organ size determination and tissue homeostasis by regulating cell proliferation and apoptosis during organ development. In mammals, upon Hippo signaling activation, two serine/threonine kinases MST (MST1 and MST2) and LATS (LATS1 and LATS2) are sequentially activated, which in turn phosphorylates the transcription co-activator Yes-associated protein (YAP) and the transcriptional co-activator with PDZ-binding motif (TAZ) via phosphorylation and thereby causes cytoplasmic retention of YAP/TAZ. In the nucleus, YAP/TAZ interact with numerous transcription factors including TEAD and thereby transactivate cancer-predisposing genes. A unique feature of the Hippo signaling is that it is regulated by a variety of signaling events such as cellular tension, cell-to-cell contact, cell polarity, and cell-extracellular matrix (ECM) interaction.

Hyaluronan (HA), a major component of the ECM, is synthesized by hyaluronan synthases and degraded by hyaluronidases. High-molecular-weight hyaluronan (HMW-HA) (> 1,000 kDa) exhibits anti-proliferative and anti-oncogenic actions by binding to its cellular receptor CD44. In contrast, low-molecular-weight hyaluronan (LMW-HA) (10-250 kDa), which is produced by hyaluronidase-mediated degradation of HMW-HA, exhibits pro-proliferative and pro-oncogenic actions by binding to CD44. However, the mechanisms underlying the size-dependent opposite bioactivities of HA remain uncertain.

In this study, we found that treatment with HMW-HA stimulates Hippo signaling. Mechanistically, the extracellular association of HMW-HA with CD44 causes clustering of the CD44 extracellular domain, which leads to interaction of intracellular CD44 with PAR1b (partitioning defective-1b)/MARK2 (microtubule affinity-regulating kinase 2). We found that PAR1b inhibits MST1 and MST2 via phosphorylation on Thr440 and Ser444, respectively. Upon HMW-HA treatment, the Hippo signaling-inhibitory PAR1b-MST complex is disrupted through CD44-PAR1b interaction. Once liberated from PAR1b, MST activates Hippo signaling. On the other hand, LMW-HA inhibits Hippo signaling by competing with

HMW-HA for CD44 binding. Therefore, this study revealed the mechanism by which hyaluronan mediates opposing cellular responses depending on its molecular size.

To evaluate the *in vivo* relevance to the HMW-HA-mediated activation of Hippo signaling, we conducted immunohistochemical analysis of hyaluronidase-2 and YAP expression in surgically isolated breast cancer specimens. We also conducted Kaplan-Meier analysis for disease-free survival rates using the TCGA breast cancer dataset. Triple-negative breast cancers with higher hyaluronidase-2 expression show poorer prognosis than those with lower hyaluronidase-2 expression. Consistently, inhibition of hyaluronidase-2 expression is associated with reduced tumorigenicity in a tumor xenograft model. Hence, perturbation of HMW-HA-mediated Hippo signaling activation contributes to cancer aggressiveness.

### 2. Inverse regulation of co-activator functions of YAP and TAZ through tyrosine phosphorylation status of Parafibromin

Parafibromin is the human (mammalian) orthologue of budding yeast Cdc73, a component of the RNA polymerase II (Pol II)-associated factor (PAF) complex. Absence of, or mutation in, the PAF components results in alterations in gene expression that can lead to deregulation of developmental programs and loss of control of cell growth and differentiation, thereby predisposing to various diseases including cancer. Parafibromin regulates multiple independent morphogen signaling pathways such as  $\beta$ -catenin signaling and Hedgehog signaling. The transcriptional platform function of parafibromin is potentiated by tyrosine dephosphorylation, mediated by SHP2 phosphatase, while it is attenuated by tyrosine phosphorylation, mediated by PTK6 kinase.

In the present study, we found that Parafibromin physically interacts with YAP and TAZ, thereby potentiating their co-activator activities toward the TEAD transcription factors. TAZ is functionally activated through binding with tyrosine-dephosphorylated Parafibromin. Furthermore, TAZ and  $\beta$ -catenin interact cooperatively with dephosphorylated Parafibromin, which synergistically stimulates the co-activator functions of TAZ and



$\beta$ -catenin. On the other hand, YAP is selectively activated through binding with tyrosine-phosphorylated Parafibromin, which does not interact with  $\beta$ -catenin and thus cannot co-activate YAP and  $\beta$ -catenin. These findings indicate that Parafibromin inversely stimulates the co-activator functions of YAP and TAZ depending on its tyrosine phosphorylation status. They also suggest that YAP and TAZ exert their redundant and non-redundant biological actions through mutually exclusive interaction with Parafibromin, which is regulated by a balance of kinase and phosphatase activities toward Parafibromin.

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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**

# Department of 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- $\beta$  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 2019, special lectures for undergraduate students were given by internationally recognized scientists, Dr. Shimon Sakaguchi (Osaka Univ.), Dr. Hiroshi Kiyono (The Univ. of Tokyo), 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 Fc $\gamma$  receptors (Negishi-Koga et al., *Nat Commun*. 2015). 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<sup>+</sup>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). 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.

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.

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 $\gamma$ 5V $\delta$ 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 $\gamma$ 5V $\delta$ 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  $\gamma$ -chain ( $\gamma c$ ) 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  $\gamma c$  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  $\gamma$ 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 $\kappa$ B $\zeta$  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. Recently, 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. This study represented an important advance in our understanding of the mechanisms underlying the immune tolerance and autoimmune diseases.

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# **Radiology and Biomedical Engineering**

## **1. Radiology**

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## **Introduction and Organization**

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

## **Clinical activities**

Clinical services on Diagnostic Radiology, Nuclear Medicine, and Radiation Oncology are provided in the centralized Clinical Radiology

Service Department in cooperation with radiology technologists and nurses.

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

In the section of Nuclear Medicine, two cyclotrons and several remote or processor-controlled automated devices are installed, which facilitate standardized procedures in the PET tracer production and the implementation of GMP in PET-related work. There are two SPECT rooms and four 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 9<sup>th</sup> 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 14<sup>th</sup> 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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Ninety eight English articles in total, including another 49, have been published from our department in 2019. Please refer to our homepage, <http://www.ut-radiology.umin.jp/publication/2018.html>



# **Radiology and Biomedical Engineering**

## **2. Biomedical Engineering**

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# Department of System Physiology

## Professor (Concurrent)

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

## Associate Professor

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

**Homepage** [http://square.umin.ac.jp/bme/research\\_Eng.html](http://square.umin.ac.jp/bme/research_Eng.html)

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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

### 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  $\text{Ca}^{2+}$  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  $\text{Ca}^{2+}$  concentrations. A relatively weak shearing force like shear stress generated by fluid flow needs the presence of extracellular ATP to induce  $\text{Ca}^{2+}$  response, and at several hundred nanomolar of ATP, intracellular  $\text{Ca}^{2+}$  concentrations increase in a shear stress-dependent manner. Generally, flow-induced  $\text{Ca}^{2+}$  responses are initiated at a locus at the cell edge and propagate throughout the entire cell in the form of a  $\text{Ca}^{2+}$  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  $\text{Ca}^{2+}$  response. Endogenously released ATP by shear stress is involved in the P2X4-mediated  $\text{Ca}^{2+}$  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  $\text{Ca}^{2+}$  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  $\text{Ca}^{2+}$  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- $\beta$ -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.

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# Department of Chemical Biology and Molecular Imaging

## Professor

Yasuteru Urano, Ph.D.

## Associate Professor

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## Assistant Professor

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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, 7 PhD students, 2 master course students, one undergraduate student and one technical staff, as of FY2019.

## Teaching activities

As for under-graduate education, our laboratory takes part in medical engineering lectures for the 3<sup>rd</sup> 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 FY2019, we have developed a red fluorescent probe for esophageal cancer detection, a fluorescent probe for prostate-specific membrane

antigen (PSMA) detection, a conjugate of avidin-protease probe for sensitive cancer detection, a photosensitizer for target cell ablation in a single-cell resolution, and a highly sensitive and stable fluorescence probe for a sialidase. The details are described below.

Regarding the red fluorescent probe for esophageal cancer detection, we developed a red fluorescent probe, EP-2OMe SiR600 by conjugating a dipeptidylpeptidase-IV (DPP-IV) substrate to SiR600, which is a red fluorescent dye developed in our laboratory. By precisely controlling the fluorescence quantum yield of the dye before and after the reaction with the enzyme by means of Photoinduced electron Transfer (PeT), it was possible to achieve a large activation ratio before and after the reaction with the enzyme, which made it possible to detect cancer with high sensitivity using clinical specimens from esophageal cancer patients. (Ref 1)

To develop a fluorescent probe for detecting prostate-specific membrane antigen (PSMA, which has carboxidase activity), we first conjugated aryl glutamate, a substrate of PSMA, to a benzene ring in the vicinity of the fluorophore via an azoformyl linker, and found that LUMO (lowest unoccupied molecular orbital) energy level was sufficiently reduced to quench the fluorescence by PeT. In addition, reaction of the probe with PMSA led to the desorption of aryl

glutamate followed by denitrogenation, which yielded a large fluorescence increase due to the liberation from PeT quenching. This probe is a first-in-class fluorescence probe for detecting PSMA activity, and it was possible to detect cancer using clinical specimens from prostate cancer patients, paving the way for the fluorescence detection of prostate cancer during surgery. In addition, the design principle of the probe may be useful for the detection of various carboxypeptidases as well. (Ref 2)

As for the probe based on avidin-small-molecule probe conjugate, a fluorescent probe that recognizes leucine aminopeptidase (LAP), a peptidase highly expressed in certain types of cancer cells, was conjugated to avidin, a protein that binds to lectins expressed on cancer cells. By using a mouse model of peritoneal dissemination of ovarian cancer, we showed that a high signal to noise ratio (S/N ratio) can be obtained. (Ref 3)

Regarding the photosensitizer for killing target cells at the single-cell level, we developed SPiDER-killer- $\beta$ -gal, which is converted to active photosensitizing form after the reaction with  $\beta$ -galactosidase and at the same time trapped by intracellular protein by the nucleophilic attack. This probe may be a particularly useful tool in cell ablation experiments to analyze the role of specific cells in complex biological processes, such as the developmental stage of animals. (Publication 4)

Regarding the sialidase probe, a highly sensitive probe was developed by conjugating a substrate recognition site to HMRef, a fluorophore developed in our laboratory, by precisely controlling the spirocyclization equilibrium before and after the reaction. A self-immolative linker was inserted between the substrate and the fluorophore to stabilize the probe and to detect the target enzyme with high sensitivity. Sialidase is highly expressed in a variety of cancers and bacteria that induce infections, so the probe developed in this study may be useful for the sensitive detection of these diseases. (Ref 5)

We also performed several collaboration works (Reference 6-7).

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# Department of Biosystem Construction & Control

## Lecturer

Takashi Isoyama, Ph.D.

**Homepage** [http://www.bme.gr.jp/bme\\_E/](http://www.bme.gr.jp/bme_E/)

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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 students, 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  $\Delta P$  control) was developed by reforming the 1/R control function. At present,  $\Delta P$  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 started. 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 shear 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

Katsutoshi Oda, 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. The division of Integrative Genomics is organized by Professor Katsutoshi Oda, and will include one Associate Professor Aya Ushiku from June 2020. 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) Analysis of molecular-targeted therapies in cancer cells
  - a. PI3K/mTOR inhibitors
  - b. PARP inhibitors, ATM inhibitors, ATR inhibitors (all of which target DNA repair pathway)
  - c. MDM2 inhibitors in TP53 wild-type cancers
  - d. Histone methyltransferase inhibitors

(3) Exploration of biomarkers for molecular-targeted drugs

- a. Evaluation of homologous recombination deficiency by using mutational signatures
- b. CDK4/6 enzymatic activities and prognosis for recurrence
- c. Classification by expression signature to predict sensitivity to immune checkpoint inhibitors

### Translational Research

(1) Todai OncoPanel and Genomic Medicine in Cancer

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

UMIN000033647

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

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

This study assesses the efficacy of olaparib maintenance monotherapy in high-grade and stage IIIC/IV ovarian cancer patients (including patients with primary peritoneal and / or fallopian tube cancer) with "BRCA-related biomarker" that is predicted by

whole-exome sequencing of fresh-frozen tumor samples.

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

## Publications

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# **Neuroscience**

## **1. Basic Neuroscience**

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# 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.,  $\beta$ -amyloid (including its binding protein CLAC), presenilin/ $\gamma$ -secretase and  $\alpha$ -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 $\beta$ -amyloid and presenilins

Using C-terminal specific monoclonal antibodies that discriminate amyloid  $\beta$  peptides ( $A\beta$ ) ending at 40th or 42nd residues ( $A\beta_{40}$  and  $A\beta_{42}$ , respectively),

Dr. Iwatsubo has performed a systematic immunohistochemical 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  $\beta$ -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  $\beta$ -amyloid hypothesis. They then focused on the mechanisms of  $\gamma$ -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  $\gamma$ -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  $\gamma$ -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  $\gamma$ -secretase (see reviews; Iwatsubo

Mol Psychiatr, 2004; Curr Opin Neurobiol, 2004). His group has also shown by establishing *in vitro*  $\gamma$ -secretase assays that sulindac sulfide, a major non-steroidal anti-inflammatory drug, directly acts on  $\gamma$ -secretase and selectively reduce A $\beta$ 42-generating activities (Takahashi et al., J Biol Chem, 2003), providing important implications to the therapeutic strategies of AD by  $\gamma$ -secretase modulation. Recently, he has established a novel method for an efficient *in vitro* reconstitution of  $\gamma$ -secretase complex, paving the way towards the structural analysis of active  $\gamma$ -secretase (Hayashi et al. J Biol Chem, 2004), and using thus highly purified  $\gamma$ -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  $\gamma$ -secretase complex by cysteine chemistry, and demonstrated that  $\gamma$ -secretase harbors a water-permeable catalytic pore (Sato et al. J Neurosci, 2006), and that substrate proteins enter the catalytic pore through the lateral gate located at the C terminal side of PS (Sato et al. J Neurosci, 2008). Thus, Dr. Iwatsubo's group started from an elegant immunohistochemical analysis of A $\beta$  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 $\alpha$ -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  $\alpha$ -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  $\alpha$ -synuclein from DLB cortices using fine biochemical techniques, purified it

to near homogeneity, and demonstrated using mass spectrometry and specific antibodies that  $\alpha$ -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  $\alpha$ -synuclein antibody is widely used as the most sensitive marker for  $\alpha$ -synucleinopathy lesions, and has characterized a wide spectrum of  $\alpha$ -synuclein pathologies in neurodegenerative disorders.

## 3. Identification of a non-A $\beta$ Alzheimer amyloid plaque component CLAC, and its precursor CLAC-P

The major component of Alzheimer's amyloid plaques is A $\beta$ , although there are a number of non-A $\beta$  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 $\beta$  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,  $\beta$ -sheet-rich amyloid deposits, underscoring the pathobiological role of CLAC in amyloid formation, and that CLAC inhibits fibrillization of A $\beta$  *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

## Professor and Head

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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 6<sup>th</sup> floor, in the West wing of the third building of the Medical School. The Department currently enrolls one professor, three assistant professors, two postdoctoral scholar, one technical staff member, seven Ph.D. graduate students, one rotating medical student, 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 $\gamma$ ) 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 $\gamma$  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<sup>2+</sup>-dependent signaling molecules process each pattern of intracellular Ca<sup>2+</sup> 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  $\text{Ca}^{2+}$ , when a neuron received various frequencies of synaptic inputs. These experiments provided evidence that CaMKII $\alpha$  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  $\text{Ca}^{2+}$  signaling, we have developed R-CaMP2, a red genetically-encoded  $\text{Ca}^{2+}$  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  $\text{Ca}^{2+}$  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  $\text{Ca}^{2+}$  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  $\text{Ca}^{2+}$ -influx while the latter was likely to be mediated at least in part by L-type voltage-gated  $\text{Ca}^{2+}$  channel activity. Thus, distinct patterns and sources of  $\text{Ca}^{2+}$  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 $\alpha$  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 $\alpha$  still remains to be demonstrated in vivo, it is intriguing to note that most active axonal process formation and elongation actually occur in the inner zone of EGL that is opposite and most distant from the interface with the pia mater (Bito, *J. Biochem.*, 2003). Most strikingly, we demonstrated that axon elongation could actively occur in an intermediate Rho activity range that enables ROCK to be weakened enough while allowing another Rho effector mDial to actively mediate its effect on actin nucleation and polymerization (Arakawa et al., *J. Cell Biol.* 2003).

Whether similar or distinct mechanisms also operate during spinogenesis and spine maturation remains to be determined, though a role for Rho and ROCK has already been postulated in control of spine complexity and spine stability. However, multiple small GTPase signaling cascades clearly seem to contribute together, in a tightly coordinated manner, to spine regulation, since many distinct classes of GEFs and GAPs have now been shown to be localized in the dendritic spines. We ourselves initially reported the

first two direct examples for PSD localization for such Rho small GTPases interacting proteins, Citron (Furuyashiki et al., *J. Neurosci.*, 1999) and Cupidin/Homer2 (Shiraishi et al., *J. Neurosci.*, 1999).

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

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

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# **Neuroscience**

## **2. Integrative Medical Neuroscience**



# Department of Child Neuropsychiatry

## Associate Professor

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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 2019, we had 7 graduate students. In addition to research training, educational program including full-year lectures of child psychiatry, case conference and journal club 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 2019 are as follows:

- Epidemiological, behavior phenotype, neuropsychological, genetic 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)
- Genomic and epigenomic analysis of ASD
- 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 psy-

chiatric social workers. In 2019, approximately 800 new patients visited our outpatient clinic, and the total visits per day were about 140.

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 400 patients with various psychiatric disorders were admitted in 2019. 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 over 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); 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  $\alpha$ -dystroglycan ( $\alpha$ -DG)-associated diseases, we identified the glycan unit ribitol 5-phosphate (Rbo5P) in  $\alpha$ -DG and showed that enzyme activities of  $\alpha$ -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  $\alpha$ -DG-associated diseases indicated that spatiotemporal persistence of functionally glycosylated  $\alpha$ -DG may be crucial for brain development. These findings provide insight into pathogenesis and therapeutic strategies in  $\alpha$ -DG-associated diseases. (Toda, T., Kanagawa, M., Kobayashi, K., Sudo, 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., Sato, N., Naruse, F.H., Matsukawa, M., Kikuchi, J., Shibata, S., Chikada, A., Nagasako, Y., Hao, A., Shinmi, J., Mitsue, A., 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., Sugiyama, Y., Sato, K., and Otsuka, J.)

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., Kadoya M., Unuma, A.)

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  $\beta$  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)

## Publication

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# Department of Neurosurgery

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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, an associate professor, 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, Wednesday 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 2019 to March 2019, 18,723 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 2019, 940 patients were admitted to the neurosurgery ward. 462 surgical procedures and 171 gamma knife procedures were performed in 2019. 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. State-of-the-art techniques including intraoperative computer-aided navigation and intravascular procedures help our continuous effort to increase the safety of surgical treatment. Some endovascular procedures are performed in our hybrid operating room with the cooperation of the operation department and the anesthesiology doctors.

Our department is affiliated with 35 neurosurgical institutions in and around the city of Tokyo including 10 university medical centers, where our residents and students are exposed to various clinical experiences. Surgical case volume in all hospitals exceeds 11,500 cases.

## Teaching activities

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

We accepted 14 residents in 2015, 4 in 2016, 16 in 2017, 5 in 2018, 7 in 2019 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

Genetic analyses were conducted to identify clinically relevant molecular markers of cerebrovascular diseases and benign brain tumors and to elucidate the pathogenic mechanisms of these diseases. Specifically, genes such as *RNF213* in moyamoya disease, *NF2* in meningioma and schwannoma, and *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. Results showed that the *RNF213* mutation is associated with not only moyamoya disease but also various intracranial artery stenoses. For *NF2* analysis in neurofibromatosis type 2, the diagnostic rate of somatic mosaicism was improved by analyzing DNA from various tissues; this revealed the phenotype characteristics of the somatic mosaic *NF2*.

### 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*, *TP53*, and histone gene mutations, 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 approaches with whole exome sequencing, RNA sequencing, expression profiling, and methylation analysis. Our particular interest lies in tumor heterogeneity and malignant progression.

To develop a novel strategy for the treatment of malignant glioma, we have isolated brain tumor initiating cells, which are supposed to be responsible for resistance to conventional therapies, from surgical specimens, and we are studying specific targeting therapy against these cells.

We have been collaborating with a basic research lab in our university and developing new 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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# Department of 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 8<sup>th</sup> 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 9<sup>th</sup> 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 (3 are from outside of UTokyo), 2 technical staffs, 8 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.

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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 2019, the Department consists of 6 faculty members above listed, 4 project researchers (part-time), 2 supporting staff members, 11 graduate students (6 in PhD program, 1 in temporary supervised program, 4 in professional degree course), 15 part-time lecturers, and 37 visiting fellows.

## Teaching activities

### 1) Undergraduate Program (Medical School)

In the winter 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, evidence based medicine (EBM), health economics, quality of care, community medicine, infection and tuberculosis control, mental health, human ecology, global health, current health policy and administration in Japan, 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, and health services research) is provided. All the above lectures are given by faculty members and part-time lectures including governmental officials and 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 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. The reports submitted are bound and made available to those students in subsequent years.

The Department also 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.

### 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 (cancer, diabetes, and osteoporosis) 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 a system of HIV/AIDS care with the introduction of highly active anti-retroviral therapy (HAART) in developing countries, since such a system involves medical, behavioral, social, and economic factors, and would inevitably become 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, and (3) epidemiological study on incidence and survival rate of children with cerebral palsy.

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# **Social Medicine**

## **2. Forensic Medicine, and Medical Informatics and Economics**



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# Department of Forensic Medicine

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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 2<sup>nd</sup> 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 3<sup>rd</sup> 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 4<sup>th</sup> Professor Shokichi Ueno discovered a complex complement. He helped foundation of national police academy for death investigators.

The 5<sup>th</sup> 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 6<sup>th</sup> Professor Ikuo Ishiyama encouraged forensic pathology. He also introduced DNA fingerprinting and PCR technique in the forensic practices.

The 7<sup>th</sup> 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 8<sup>th</sup> 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 9<sup>th</sup> 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.

## Education

As for under-graduate education, our department provides lectures for the 4<sup>th</sup> year medical students, Free Quarter training course for the 3-4<sup>th</sup> year medical students, and Elective Clerkship learning for the 5<sup>th</sup> 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.

## Publications

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# Department of Biomedical Informatics

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## Assistant Professor

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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**



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# 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, 9 staff members, and 40 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 2019, a total of 1,803 patients were newly admitted to our hospital ward of 61 beds. The average duration of hospitalization was 10.4 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, 27 patients underwent heart transplant (total 138 cases). In March 2014, our facility was also authorized to perform lung transplantation. Coronary angiography was performed in 738 patients, of which 349 patients underwent interventional procedures. CT coronary angiography and cardiovascular MRI were performed in 440 and 135 patients, respectively. With regard to arrhythmias, there were 319 cases of catheter ablation, 112 cases of implantation or replacement of pacemakers and other specialized pacemaker devices, including 20 cases of implantation or replacement of implantable cardioverter-defibrillator and 25 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 189.1 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 pulmonary

hypertension, congenital heart disease, valvular heart disease, cardiomyopathy, arrhythmia, Marfan's syndrome, cardiac amyloidosis, cardiac sarcoidosis, chronic myocarditis. 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. Nitric oxide and endothelial function
3. Interplay between organs, cells, and molecules in chronic inflammation
4. Mechanisms underlying cardiorenal association
5. Role of hypoxia signaling in cardiovascular diseases
6. Genetic analysis of inherited cardiomyopathy
7. Experiments on pathophysiology of cardiomyopathy using human iPS cells
8. Investigation of disease pathophysiology and development of novel therapies (severe heart failure, cardiac transplantation, congenital heart disease, etc.)
9. New treatments for structural heart disease
10. Diagnosis and treatment of Marfan syndrome and adult congenital heart disease
11. New treatments for pulmonary hypertension
12. New treatments for congenital heart disease
13. Aerobic threshold and cardiac rehabilitation
14. Imaging techniques (echocardiography, MRI, CT, and SPECT) in cardiovascular diseases
15. Epidemiology and prevention of cardiovascular disease
16. 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, 17 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 13<sup>th</sup> 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 3<sup>rd</sup> 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 2019

1. Primary lung cancer	464
2. Interstitial pneumonia	87
3. Respiratory infections	18
4. Pneumothorax	10
5. COPD	9
6. Non-tuberculous mycobacterial infections	8
6. Malignant mesothelioma	7
7. Pulmonary aspergillosis	6

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 4<sup>th</sup> year medical students, clinical clerkship for 5<sup>th</sup> year medical students, and clinical lectures for 5<sup>th</sup> and 6<sup>th</sup> year medical students. During elective clerkship for 5<sup>th</sup> 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 5<sup>th</sup> 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. 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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# Department of Gastroenterology

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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 field of liver, pancreato-biliary and digestive canal. It is comprised of a professor, 3 lecturers, 21 associates, 9 fellows, 72 graduates and other visiting researchers including students from abroad. A number of others are under a temporary transfer in- and outside the country. The North and South wings on the 11th floor of Ward A have provided core hospital

rooms for the department. At present, 9th floors of Ward B also take important part for providing rooms for inpatients. Laboratories of the department are scattered in 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 2,900 in total per year. We receive about 110 new patients in and out of the hospital each week, with an average hospital stay of 9.4 days. Resident, junior and senior staff members bear the responsibility for a medical management of each inpatient, in collabora-

tion with subspecialty groups concerned. The staff members examine about 5,300 outpatients with various digestive diseases in a month. Professor's ward round is performed on Monday and Wednesday mornings. 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 (~600 cases in 2019). Number of treatments for hepatocellular carcinoma treatments, represented by percutaneous radiofrequency ablation, nearly 250 cases per year, showing one of the greatest achievements in the field. 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 the evaluation of increasing non-alcoholic steatohepatitis patients. In addition, nearly 100% cure for the HCV hepatitis can be achieved now by the use of oral anti-viral agents instead of IFN therapy. This will be especially beneficial for the elderly patients and advanced fibrotic patients.

In the pancreato-biliary field, about 1000 ERCPs are performed annually. The cumulative number of endoscopic treatments of bile duct stones using endoscopic papillary balloon dilation (EPBD) and endoscopic sphincterotomy (EST) exceeds 1,000 cases. Endoscopic placement of a metal stent is the standard of care for malignant obstructive jaundice and our group has led the development of covered metal stents. Pancreatic interventions such as pancreatic stenting, cystic drainage and stone extraction are also performed, which are often technically challenging. In addition to these conventional ERCPs, we have performed a number of advanced endoscopic procedures such as 1,000 balloon-assisted ERCPs for surgically altered anatomy cases, 1,000 EUS-FNAs and 300 EUS-guided interventions. In combination with these interventions, we have conducted clinical trials of chemotherapy for advanced pancreatobiliary cancer.

In the gastrointestinal field, ESD (endoscopic submucosal dissection) is performed as a curative endoscopic treatment for neoplasms in esophagus, stomach or colon (approximately 450 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. Double-balloon endoscopy and capsule endoscopy enabled the examination of whole small intestines (approximately 320 cases in 2017). 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 new molecular-targeting drugs.

On 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 370 cases of esophageal cancer, 760 cases of gastric cancer and 1300 cases of colorectal tumor annually, and half of them are treated endoscopically. Using these resected tissues, we perform various basic studies in order to feed the new finding back to actual clinical activities.

## Educational Activities

The undergraduate medical students regularly take the clinical lectures of the staffs in our department. Several courses of practical teaching are also provided for the students. Particularly, in the Clinical Clerkship program during the fourth 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 period, the students make the summary presentation of the patients and also outline the articles from world's leading medical journals.

The residents of internal medicine participate in the

training of our department for 1-4 months in the first year. They learn the knowledge of therapeutics and diagnostics in gastroenterology as well as general internal medicine. Our department deals with the training curriculum as a medical specialist of internal medicine. The residents in the course are supported to experience some diseases in the gastrointestinal field. The residents who major in gastroenterology as subspecialty take the expert training of gastroenterology in the affiliated hospitals for several years.

The students of Department of Gastroenterology in the Graduate School of Medicine perform high standard of medical research in the basic or clinical field for 4 years. Currently, 72 students are in our department.

## Research Activities

Both basic and clinical researchers are equally encouraged, on 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, 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, in order to eventually translate the basic results into clinics.

Various clinical activities are recorded in database and analyzed. Studies oriented for evidence-based medicine are highly appreciated. Recent studies include radiofrequency ablation for liver metastasis of colorectal cancer, impact of metabolic factors in hepatocarcinogenesis. We have also designed many clinical trials as follows; molecular target drugs for advanced hepatocellular carcinoma, SNPs analyses for anti-viral treatment for hepatitis C, new chemotherapeutic regimens for advanced pancreatobiliary cancer, duration of antibiotics after endoscopic biliary drainage for acute cholangitis, balloon

endoscope-assisted ERCP for surgically altered anatomy, new chemotherapeutic regimens for advanced pancreatic cancer or biliary tract cancer, efficacy of polyglycolic acid sheets for artificial endoscopic ulcers, 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 suffering from malignant diseases. Furthermore, we aim to find the new aspects of diseases and create a new strategy against it, which are based on clinical, basic, and epidemiological studies in our area.

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# **Internal Medicine**

## **2. Medicine II**

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## Introduction and Organization

The Department of Nephrology and Endocrinology is one of the major divisions in the Department of Internal Medicine of the University of Tokyo, which covers nephrology, hypertension, and endocrinology, and also renal diseases associated with diabetes mellitus, cardiovascular diseases, collagen diseases and so on. Usually we have up to 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-HCO<sub>3</sub> 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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# Department of Diabetes and Metabolic Diseases

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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 28 beds mainly on the 12th floor of the North Wing Ward A of the University of Tokyo Hospital, and took care of 611 new inpatients per year. Besides the staffs listed above, our division holds faculties in branches, for example, Department of Prevention of Diabetes and Lifestyle-Related Diseases (Project Professor: Dr. Takashi Kadowaki), 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 Associate Professor: Dr. Masato Iwabu [until Jan 2020]), Genomic Research Support Center (Project Associate Professor: Dr. Nobuhiro Shojima), Ubiquitous Health Informatics (Project Associate Professor: Dr. Kayo Waki [until Aug 2019]),

Department of Healthcare Information Management (Associate Professor: Dr. Kayo Waki [since Sep 2019]), Department of Clinical Laboratory (Lecturer: Dr. Makoto Kurano), Division for Health Service Promotion, The University of Tokyo (Assistant Professor: Dr. Sachiko Okazaki) and Center for Epidemiology and Preventive Medicine (Project Assistant Professor: Dr. Yukari Masuda). With all these staffs, we actively instruct and teach the residents and medical school students; annual evaluation of the teaching skill by the students always rates our department within the three places of the top. In addition, there are 12 students of Graduate School in our division. With all these 52 members, we enthusiastically work on the research activities, which lead to the outstanding contributions in the field of metabolism.

## Clinical activities

Based on the update clinical evidences and with the experienced skills, we provide patient-centered medical services in the highest quality. We have outpatient clinics from Monday through Friday, and have been following approximately 164 patients per day (total 39,802 patients per year). On the inpatient ward, we not only take care of around 28 patients in our division as mentioned above, but also provide a sophisticated management to all patients suffering from metabolic diseases, especially diabetes mellitus. Diabetes mellitus, metabolic syndrome, dyslipidemia and obesity disease are becoming more prevalent in Japan, and lead to complications including nephropathy, retinopathy, neuropathy and cardiovascular diseases. Thus, in collaboration with other departments, we optimize the treatment of each patient.

We provide the educational classes to the patients every weekday in the inpatient ward, and also give lectures twice a week in the outpatient unit. In addition, in collaboration with ancillary staffs of our hospital, we provide patients well-reasoned instructions regarding nutritional management, excise therapy and medical therapy.

The weekly official activities of our department consist of the pre-round case conference and the Ward Round by the Professor on Monday. We also hold a weekly case conference by the consultation group

staffs.

## Teaching activities

As for medical student education, our department takes a part in systemic lectures for the 4th year medical students, bed-side learning and clinical clerkship for the 5th year medical students, and clinical lectures for the 6th year medical students.

In systemic lectures, comprehensive presentation for the understanding of basic knowledge about the concept, pathogenesis, diagnosis and treatment of common metabolic diseases is performed.

In clinical lectures, we present clinical cases of important diseases such as diabetes mellitus, and try to discuss with the students several points for planning the diagnosis and treatment in collaboration with the faculties of the Departments of Nephrology, Cardiology, and Ophthalmology.

During the period of clinical clerkship, the students have opportunities to experience the daily clinical care with junior and senior residents as well as with the Faculty members. Each student can learn how to do history taking, perform physical examinations and make the actual plans for the diagnosis and treatment. In addition, we arrange the program so that the students can experience the clinical practice and learn the disease itself more profoundly. One faculty and one senior-resident always instruct one student. Especially, Diabetes Clinical Seminar and oral examination that lead to profound understandings of the metabolic diseases are regularly provided by the Professor.

As for the post-graduate education, attending doctor (staff) and senior resident instruct the junior residents. We provide advanced teaching through the seminars and grand conference.

## Research activities

There are several laboratories in our departments; collaborating with each other or with other departments, we focus on the molecular mechanisms of the metabolic diseases and the establishment of the novel therapeutics.

1) Molecular mechanisms of type 2 diabetes

We have been attempting to elucidate the mechanisms

underlying the development of type 2 diabetes at the molecular and genetic levels. To this end, in collaboration with RIKEN and several cohorts, we explored the comprehensive catalog of genomic variations to identify variations conferring susceptibility to type 2 diabetes in the Japanese population. We are also exploring the signal transduction pathways and physiological roles of insulin and adipokines in various tissues and the mechanisms of insulin secretion under the normal or pathological conditions, such as diabetes and obesity disease, using a number of transgenic and knockout animal models, in parallel with information obtained by whole-genome analysis of human patients. In particular, we are interested in the physiological and pathophysiological functions of adipokines secreted by adipocytes, including adiponectin, and the signal transduction pathway of adiponectin through the receptors, AdipoR1 and AdipoR2, that we discovered and characterized. We have also identified “AdipoRon” as an adiponectin receptor agonist, which will contribute to the development and optimization of AdipoR-targeted therapeutics. In addition, we have been successfully unraveling the molecular mechanisms of  $\beta$  cell proliferation and inter-tissue communication of glucose metabolism in obesity disease and type 2 diabetes. Recently, we are investigating brown and white adipocyte-specific transcriptional and epigenetic regulations in obesity. We believe that these findings and research activities will lead to novel therapeutic strategies for diabetes and the metabolic syndrome.

## 2) Pathophysiological roles of lipid storage and atherosclerosis

Our aim is to clarify the significance of metabolic risk factors in the onset and development of atherosclerosis. We are currently investigating the pathophysiological roles of lipid storage in obesity disease, fatty liver, diabetes, hyperlipidemia and atherosclerosis using strategies of molecular biology and genetic engineering techniques. Utilizing the animal models of lipid disorders and molecular biological technique, we are analyzing the roles of lipid transporters, nuclear receptors and the anti-oxidative proteins on the lipid disorders and atherosclerosis. We are currently interested in the cholesterol and lipid absorption from the intestine and lipid

handling in the cells.

## 3) Clinical trials and epidemiological studies

We are conducting clinical trials and epidemiological studies including “Japan Diabetes Optimal Integrated Treatment study for 3 major risk factors of cardiovascular diseases (J-DOIT3)” follow-up study, “Japan Diabetes compREhensive database project based on an Advanced electronic Medical record System (J-DREAMS)”, systematic reviews and meta-analyses with a focus on important issues such as metabolic syndrome, and investigator initiated clinical trials targeting for a new class of anti-diabetic agents.

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# Department of Hematology and Oncology

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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 8 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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# Department of Infectious Diseases (Internal Medicine)

## Professor

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## Associate Professor

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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 11<sup>th</sup> 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 13<sup>th</sup> 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 CDI infection

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# Department of Stress Science and Psychosomatic Medicine

## Associate Professor

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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, and 5 adjunct professors, and other members are 4 senior residents, 13 graduate students, and 5 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 2019 April to 2020 March, overall 2,061 patients (71 individuals) were admitted to the ward, many of whom were eating disorder patients. Outpatient clinic is attended on every morning and afternoon in three consultation rooms by approximately fifteen physicians. During 2019 April to 2020 March, the numbers of the new outpatients and of the overall outpatients in our department were 196 and 4,876, 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.

Seven graduate students and 5 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**

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# Department of Transfusion Medicine

## Professor

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## Associate

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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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## 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

## Professor

Yutaka Osuga

## Associate Professor

Yasushi Hirota

**Homepage** <https://www.h.u-tokyo.ac.jp/patient/depts/jyoseigeka/>

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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

## Professor

Tomoyuki Fujii

## Associate Professor

Kaori Koga

**Homepage** <https://www.obstetrics-htu.jp/>

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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 19 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 200 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

**Homepage** [http://www.h.u-tokyo.ac.jp/patient/depts/a\\_joseika02/index.html#reproduction](http://www.h.u-tokyo.ac.jp/patient/depts/a_joseika02/index.html#reproduction)

## 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

## Professor

Akira Oka, M.D., Ph.D.

Naoto Takahashi, M.D., Ph.D. (Department of Pediatric and Neonatal Intensive Care)

## Associate Professor

Yutaka Harita, M.D., Ph.D..

## Lecturer

Ryo Inuzuka, M.D., Ph.D., Satsuki Kakiuchi, M.D., Ph.D. (Department of Maternal, Fetal and Neonatal Medicine), Youichirou Hirata, M.D., Ph.D., Mitsuteru Hiwatari, M.D., Ph.D. (Department of Cell Therapy and Transplantation Medicine), Hikoro Matsui M.D., Ph. D.

## Associate

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(As of March 31, 2020)

**Homepage** <http://square.umin.ac.jp/ped/>

## 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, 1 associate

professor, 4 lecturers, 2 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

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. In general ward of the Pediatric Medical Center, we treat variety of patients with diseases, such as hematological/oncological disorders (acute leukemia, neuroblastoma, rhabdomyosarcoma, hepatoblastoma, brain tumors, etc.), cardiac disorders (congenital heart diseases and Kawasaki disease), neuromuscular disorders, immunological/allergic disorders (common variable immunodeficiency, chronic granulomatous disease and bronchial asthma), renal and urinary tract diseases (nephrotic syndrome, chronic glomerulonephritis, purpura nephritis and renal and/or urinary tract anomalies), 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 neurological 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. 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 staff members and the visiting lecturers give lectures of general pediatrics to the second year students. The third year students have clinical clerkship in the inpatient ward for 2 weeks. During



bedside learning, teaching sessions on variety of pediatric fields are held every day. We also offer an elective clinical clerkship course for selected students in their fourth year. In the outpatient learning of the fourth year students, students take histories and perform physical examinations of patients under the supervision of the teaching staff. On the last day of clinical learning, the Professor and an Associate Professor evaluate the students' achievements. We also provide 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 multi-disciplinary 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 cardio-

myopathy. 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.

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# Department of Pediatric Surgery

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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, one lecturer, five 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 6 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

In the clinical ward, there are approximately 20 patients who are taken care of by junior, senior and chief residents of our staff. Because senior and chief residents are very experienced, they team up with a junior resident, give instructions as to the assessment of the patient's problem, making of future plans, and help the residents with various procedures. Very important issues are discussed and decisions are made in weekly professor's round.

## 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

Various studies have been done over a wide range of field, such as clinical observational studies or basic molecular studies.

- 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 Article

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# **Surgical Sciences**

## **1. Surgery**

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# Department of Thoracic Surgery

## Professor

Nakajima, Jun

## Assistant Professor

Sato, Masaaki

Nagayama, Kazuhiro

Kitano, Kentaro

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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 researches 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 in December 15, 1964 as the first department of this field along with the cardiovascular surgery in the Japanese national universities. Since then 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 researches, and education of the medical students, postgraduates, and the surgical residents in our university.

## Clinical activities

Five of six staffs (Nakajima J, Sato M, Nagayama K, and Kitano K, and Konoeda C), 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 2018, Ministry of Health, Labour and Welfare documented that number of deaths from malignant neoplasms was approximately 386 thousand out of 1.36 million total deaths in Japan. Of them, 74 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), i.e. lobectomy and lymphadenectomy through thoracoscopy: Since 2015, more than 90% of patients with NSCLC has undergone thoracoscopic surgery in our department. Researches on less-invasiveness, oncological advantage of the thoracoscopic surgery are thus actively done.

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 41 lung transplants (including 7 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 researches

Main subjects of current research at present include basic and clinical studies on the malignant neoplasms in the thorax including lung cancer and thymic tumors, and transplantation of the thoracic organs. The following items are the major themes under research in our department:

- (1) Minimally invasive surgeries for thoracic malignant neoplasms.
- (2) Navigation techniques for finding out small pulmonary lesions through thoracoscopy.
- (3) Imaging analysis of lung lung adenocarcinoma



- (4) Global analysis of oncogenes and suppressor genes associated with lung cancer.
- (5) Application of new fluorescent agents for diagnosis of lung cancer.
- (6) Immunotherapy for lung cancer.
- (7) Analysis on mechanisms of acute or chronic rejection of the allogeneic lung and trachea after allogeneic transplantation.
- (8) Regeneration of the de-cellularized allogeneic lung with autologous cell seeding
- (9) Research on extracorporeal membranous oxygenation for bridge use to lung transplantation

### Selected publications (2019)

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# Department of Cardiac Surgery

## Professor

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## Associate Professor

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## Lecturer

Haruo Yamauchi, M.D., Osamu Kinoshita, M.D., Mitsutoshi Kimura, M.D.

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Akihiro Masuzawa, M.D., Shogo Shimada, M.D., Ando Masahiko, M.D.,

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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 5<sup>th</sup> 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 5<sup>th</sup> floor, and pediatric patients in the South Wing of 2<sup>nd</sup> 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 13 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 2020, 145 cases of heart transplantation including 14 pediatric patients and 347 cases of ventricular assist device (VAD) implantation including 217 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 2<sup>nd</sup> 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 1<sup>st</sup> and

2<sup>nd</sup> grade. Joint lectures with the Cardiology Department are scheduled 3<sup>rd</sup> through 4<sup>th</sup> 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 3<sup>rd</sup> 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 9-10<sup>th</sup> 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 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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# Department of Gastrointestinal Surgery

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## Bariatric & Metabolic Care (Social Cooperation Program)

### Project Associate Professor

Susumu Aikou M.D., Ph.D.

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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 160 gastric and 80 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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<http://www.h.u-tokyo.ac.jp/patient/depts/1512ishokugeka/index.html>

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## Introduction and Organization

The Hepato-Biliary-Pancreatic Surgery Division, Artificial Organ and Liver Transplantation Division, Department of Surgery (HPB Surg Division) 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 Tokyo University, and organ-specific medication has been progressively recommended, 2nd Dept of Surg has been replaced to HPB Surg Division since June 1st, 1998.

## Clinical Activities

Our division deals with patients with hepato-biliary-pancreatic malignancies, liver cirrhosis, and HBP benign diseases. We specialize in hepatectomies for HCC and colorectal metastasis, Whipple's procedure, and liver transplantations, mainly from living donors. The overall number of operation is about 500/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 students, and clinical lectures and bed-side practice for M3 and M4 students, in accordance with other surgical and non-surgical departments. Since 2013, the bed-side practice was rearranged as "Clinical Clerkship," more practical medical training than conventional "Bed-Side Teaching". Our division precedes Clinical Clerkship in the Tokyo University Hospital, and recommends students to aggressively attend the surgical activities.

Clinical Clerkship is designed to consist of 2 parts; 2 weeks clinical practice in Tokyo University 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 Hepato-Biliary-Pancreatic Surgery and liver transplantations. 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, and preoperative navigation for hepatic surgery.

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# Department of Urology

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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. 1481 operations were performed in 2019. The numbers of main operations are adrenalectomy 16, nephrectomy 27, partial nephrectomy 44, nephroureterectomy 20, radical cystectomy 19, radical prostatectomy 151, transurethral resection of the bladder tumor (TUR-Bt) 211, transurethral resection of the prostate (TUR-P) 9, and Robot assisted surgery 200 (radical prostatectomy 151, partial nephrectomy 40, radical cystectomy 9).

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 24,896 patient-days from January 2019 to December 2019.

## Teaching activities

Systematic urological lectures are provided for second year medical students. Both clinical lectures and bed side teaching are scheduled for third and fourth year medical students. Thirteen times of systematic lectures are performed by professor, associate professors and instructors concerning their specialties.

Bed side teaching is concentrated on practical care of the patients. Teachers give lectures mainly regarding pre- and post-operative management, indication of operation, surgical anatomy and surgical techniques.

## Research activities

There are 9 research themes for research as below. The basic principles for research are program in surgical techniques and therapy for incurable diseases, which include advanced cancer, renal insufficiency, sexual dysfunction, and interstitial cystitis. We have published approximately 50 English papers every year.

Renal tumor

Urolithiasis

Kidney Transplantation

Prostate diseases

New surgical technique

Urinary disturbance/ Female Urology

Andrology

Virology

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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, one Associate Professor, two 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 544 surgically treated inpatients in the year of 2019. 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

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# Department of Vascular Surgery

## **Associate Professor and Chief of Vascular Surgery**

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## **Lecturer**

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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

## Professor

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Mayumi Harada M.D., Ph.D. Arisa Morizono M.D.

## Homepage

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### Organization

Our section is staffed by one professor, one lecturer, and six 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 addition to treatment for malignant cases of these diseases, we perform surgical procedures 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.

625-630.

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# **Surgical Sciences**

## **2. Sensory and Motor System Medicine**

# Department of Dermatology

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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 six 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.

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# Department of Plastic and Reconstructive Surgery

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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

## Professor

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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. Professor Takato had established Tissue Engineering Division in the University of Tokyo Hospital and our department has an endowment department: Depart-

ment of Cartilage and Bone Regeneration (FUJI SOFT Inc.). The department has 1 associate professor, 1 assistant professor, and several graduate students. These staffs are focusing on translational research works in maxillofacial regions.

## 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.

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 chilooplasty and palatoplasty for cleft lip and palate patients, bone grafting in alveolar cleft, orthognatic surgery of orofacial deformities, fixation of orofacial fractures, resection of malignant tumors combined with reconstruction surgery.

Peculiarity of our treatment strategy is team approach that consists of oral and maxillofacial surgeons, orthodontists and prosthodontists. In our department, patients with congenital dento-facial deformity are treated by utilizing several techniques such as distraction technique, autologous bone graft technique, and the original artificial bone graft technique in addition to orthognatic surgery. The original bone graft is made

from patient's three dimensional images of CT data and this technique is now applied for patients.

## Education

Teaching activities are divided into two parts; for undergraduate medical students and for postgraduate dental students. For undergraduate students, we make 5 systematic lectures in their second year of specialized course, and one lecture and one week bedside learning in final year. Through these curriculums, we demonstrate the characteristics and treatments of the diseases in oral-maxillofacial region. Teaching is focused on following points; congenital anomalies such as cleft lip and palate and branchial arch syndromes, dentofacial deformities caused by developmental and acquired problems, surgical resection and functional reconstruction of benign and malignant tumors, temporomandibular joint disorders, inflammation and maxillofacial trauma. Minimum dental knowledge concerning jaw movement, tooth pain, periodontal disease, malocclusion and dental restorations are instructed.

For postgraduate dental students, we have two-year-resident course. This course aims to train for a wide range of dental treatments and to learn about medical cares. Various specialists instruct dental treatments for them in outpatient clinic. Dental caries treatments, periodontal cares and applications of dentures are instructed. Tooth extractions and orthodontic treatment are instructed by oral surgeons and orthodontists. Medical cares in the ward are taught by medical doctors and oral surgeons.

After two-year residential course, research training at postgraduate school is positively recommended. Our aim for education of clinician is to raise up specialists mastered both clinic and research skills.

## Research

Our research project consists of clinic and basic sections. Each research themes are closely related on the aim of clinical improvement.

The main projects are as follows.

Clinical research:

- 1) Treatment of facial deformities in patients with cleft lip/palate and/or congenital anomaly



- 2) Treatment of jaw deformity, oral and maxillofacial traumas and temporomandibular disorders
- 3) Treatment of head and neck cancer
- 4) Distraction osteogenesis of maxillofacial skeleton using distractor
- 5) Treatment of facial deformities in patients with cleft lip/palate
- 6) Clinical study for safety and efficacy of transplantation of implant-type tissue-engineered cartilage for cleft lip-nose patients
- 7) Speech disorder in patients with cleft lip/palate
- 8) Growth and development in patients with cranio-maxillofacial anomaly
- 9) Evaluation of treatment in patients with cleft lip/palate
- 10) Surgery, chemotherapy and radiotherapy for head and neck cancer
- 11) Orthognathic surgery in patients with jaw deformity
- 12) Computer assisted surgery using computer vision and augmented reality
- 13) Evaluation of treatment in temporomandibular disorder patients
- 14) Repair and occlusal reconstruction by regenerated bone in oral and maxillofacial area

#### Basic and experimental research:

- 1) Regeneration of bone and cartilage in oral and maxillofacial area by regenerative medicine
- 2) Basic research for producing implant-type tissue-engineered cartilage using human cells
- 3) Cartilage regenerative research using iPS cells
- 4) Role of cell cycle-related molecules in control mechanism of osteochondral cell differentiation
- 5) Role of transcription factors in pluripotency of mesenchymal cells
- 6) Bone and cartilage regeneration using bone marrow mesenchymal stem cells
- 7) Epigenetic abnormalities of oral cancers and premalignant lesions
- 8) A study on the involvement of tumor associated macrophages in immunosuppression mechanism of oral squamous cell carcinoma

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(Original articles, Case reports)

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(Patents)

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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 3000 new outpatients are seen every year in our hospital, which has a total of 30 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 6400 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 bronchoesophagological 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  $\gamma$ -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: human temporal bone pathology, electron microscopic study in animal models, gene therapy, protein transduction, and nanotechnology
- 2) Speech perception and language development in deaf children.
- 3) Analysis of balance disorders using vestibular function tests
- 4) Development of novel diagnosis methods for balance disorders
- 5) Development of novel therapeutic methods for balance disorders by galvanic vestibular stimulation
- 6) Predicting and elucidating the pathogenesis of vestibular disorders using machine learning
- 7) Establishment of animal models of vestibular diseases and development of treatments
- 8) Hair cell physiology and pathology and introduction of hair cell regeneration in the auditory and vestibular end organ.
- 9) Clinical neurophysiology of the facial nerves focusing on degeneration and regeneration in patients.
- 10) Therapeutic effects of growth factors on facial nerve and laryngeal regeneration after injury
- 11) Analysis of olfactory system in development, injury and aging.
- 12) Metabolic conversion of odorant molecules by nasal mucus

- 13) Analysis of eosinophilic chronic sinusitis using human samples and animal models
- 14) Pulmonary inflammatory responses by contrast agent aspiration
- 15) Swallowing mechanisms using pathological and electrophysiological analysis and VR system
- 16) Evaluation of swallowing physiology with pharyngo-esophageal high-resolution manometry
- 17) Esophageal Motility in Neuromuscular Disorders
- 18) Kinetics of vocal cord movement using high-speed video system
- 19) Histochemical, molecular biological, and genome analysis of head and neck cancer

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

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# Department of Rehabilitation Medicine

## Professor

Nobuhiko Haga, M.D.

**Homepage** <http://todaireh.umin.ne.jp>

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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. Seventeen students have entered the graduate school by 2016, and thirteen 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 30 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) 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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# **Surgical Sciences**

## **3. Vital Care Medicine**



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# Department of Anesthesiology

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## Introduction and Organization

The Department of Anesthesiology was established in 1952, the oldest department specialized in anesthesiology in Japan. Currently, our department has 29 faculty staffs, 6 graduate students and 14 residents. We introduce the activities about Teaching, Research and Clinical work of our department.

## Clinical activities

Our clinical services include perioperative management for patients undergoing surgeries, treatment for patients suffering acute / chronic pain, and palliative care for patients with malignancies.

Number of cases undergoing surgery is increasing in our hospital and annual number of surgery cases exceeds 11,000. Recently, the number of high risk or

geriatric patients is increasing. Especially surgery for organ transplant, such as heart, liver and lung requires tight and meticulous anesthetic care. Our aim is to provide optimal perioperative care including proper preoperative assessment of patients, efficient plan for intraoperative management, meticulous intraoperative and / or postoperative care. We are a part of perioperative management team established in our hospital recently to play pivotal role in perioperative patient care. Especially for patients with multiple comorbidities, we provide preoperative assessment / consult clinic and accept 1,600 patients annually. Pain clinic services are provided for outpatients (including patients in the ward of the other departments) on a daily basis in all areas of diseases accompanied with pain. From April 2019 to March 2020, the number of ambulatory patients was about ten thousands; two

hundreds and seventy of those were newcomer patients. Currently we have one bed in the ward. We take care 40 patients in our ward and approximately 100 in other wards annually, with multidisciplinary approach in collaboration with neurologists, psychiatrist, and orthopedists. Our palliative care team manages varied somatic symptoms and psychological distress of inpatients and outpatients with cancer. Further, we manage the “cancer treatment-related chronic pain management” outpatient clinic and also the second opinion outpatient clinic for cancer pain patients with advanced and terminal cancer stages.

## Teaching activities

We give lectures for fourth year medical students and provide clinical education (Clinical Clerkship) for fifth and sixth year medical students on a man-to-man basis with our faculty staff members. The lectures of the last year were the history of anesthesia, the mechanisms of anesthesia, inhalational anesthesia, intravenous anesthesia, anesthesia and respiratory/circulatory system, the balance of body fluid, acid-base balance, muscle relaxants, management of the patient during anesthesia, monitoring, resuscitation, pain clinic and the physiology and the management of pain.

The curriculum of Clinical Clerkship consists of three major contents: learning a practice of anesthetic management for patients undergoing surgeries, observing a practice of pain management for outpatients suffering from intractable pain, and interactive lectures on specific topics. During the practice of anesthetic management, we teach students how to evaluate patients in the perioperative period. Through the practice of pain management, we teach students causes of intractable pain as well as treatment of pain including nerve block, functional therapy, and cognitive-behavioral therapy. We provide 5 mini-seminars that cover essential knowledge of clinical anesthesia for medical students, each of them entitled “introduction to anesthesiology”, “airway management”, “central venous catheterization”, “spinal anesthesia” and “pain clinic”. Moreover, students can experience procedures of tracheal intubation, central venous catheterization and spinal anesthesia using simulators. Each student is required to submit a report or a case that summarizes the procedures and medicine

applied perioperatively. We discuss the contents of the reports and summaries with students at the end of Clinical Clerkship, for their further understandings.

## Research activities

We have seven research groups and their fields include respiration, circulation, pain, immune system and shock.

These are recent major subjects of our research.

- 1) A role of cytokine signaling in acute lung injury
- 2) Evaluation of optimal ventilatory strategy for respiratory failure
- 3) Modulation of immune system by anesthetics
- 4) Signal transduction pathway related to apoptosis activated by sepsis or ischemia-reperfusion
- 5) Pathophysiology of shock
- 6) A role of lipid mediators in organ damage mediated by ischemia-reperfusion injury
- 7) A role of lipid mediators in the formation of hyperalgesia
- 8) Antihyperalgesic and antipruritic effects of alpha 2-adrenergic agonists
- 9) A role of spinal microglial cells in the development of inflammation-mediated neuropathic pain
- 10) Spinal contribution for analgesic pathway
- 11) Mechanism of Pruritoceptive and Neurogenic Itch
- 12) Genetic analyses of pain intensity and opioid sensitivity in clinical pain patients
- 13) Analysis of electroencephalography during general anesthesia
- 14) Clinical evaluation of neurological sequelae after cardiac surgery
- 15) Retrospective analysis of large administrative database to explore rare complications related to anesthesia and / or association between anesthetic drug and postoperative outcome
- 16) Effect of anesthetics on glucose metabolism *in vivo*
- 17) Role of new plasma substitutes on hemorrhagic shock
- 18) Mechanisms of chemotherapy-induced neuronal dysfunction

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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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# Department of Mental Health

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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, 10 doctoral course students, 2 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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# Department of Biomedical Ethics & Department of Health Promotion Sciences

## **Professor**

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

## **Associate Professor**

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

## **Lecturer**

Eisuke Nakazawa, Ph.D.

## **Research Associate**

Keiichiro Yamamoto, Ph.D.

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

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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. Atsuaki Gunji became the second professor of the department. During Dr. Gunji's tenure, two major research projects were undertaken. One was "The effects of physical activity and inactivity on health." From 1990, a 20-day bed rest human experimental study was conducted every year in the context of an international cooperative research project that was supported by government grants. The other project concerned health care systems, especially health care economics and the quality of hospital care.

In 1996, the Department of Health Administration developed into two departments: the Department of Health Economics and the Department of Health

Promotion Sciences. Both were established as departments of the Graduate School of Medicine. In 1998, Dr. Yasuki Kobayashi became the professor of the Department of Health Economics. He conducted research into health care delivery systems in Japan. In 2001, he moved to the Department of Public Health. From 1996 to 2002, Dr. Kiyoshi Kawakubo took charge of the Department of Health Promotion Sciences as the associate professor.

In June 2002, Dr. Akira Akabayashi became professor of the Department of Health Economics. Professor Akabayashi's area of research is biomedical ethics. In April 2003, the Department of Health Economics was restructured and named the Department of Biomedical Ethics. From 2007, Dr. Jung Su Lee became the associate professor and took charge of the Department of Health Promotion Sciences. In 2017, Dr. Yoshiyuki Takimoto acceded to the chair of the Department of Health Promotion Sciences. In 2019, the Department of Health Promotion Sciences was consolidated into the Department of Biomedical Ethics.

Staff members of the department include a



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

We have six department graduate students. Five of them are doctoral program students.

In this annual report, the organization and teaching activities are reviewed followed by an explanation of research activities.

## Teaching activities

Our departments highly prioritize the teaching and guidance of graduate students and their research activities. Eighteen bachelor theses, twenty-two master theses, and eleven doctoral dissertations were completed between April 2004 and March 2020. Our department's staff members are also responsible for the following undergraduate and graduate courses.

### Undergraduate Courses

#### Required courses

- 1) Introduction to Biomedical Ethics (Lecture)
- 2) Biomedical Ethics I (2 credits, lecture)
- 3) Theory and Science of Health Behavior (2 credits, lecture)
- 4) Seminar in Public Health Science II (2 credits, seminar)
- 5) First-Year Seminar for Natural Science Students (2 credits, seminar)

#### Elective courses

- 6) Integrated Lecture of Clinical Medicine, Biomedical ethics (Lecture)
- 7) Integrated Lecture of Clinical Medicine, Biomedical ethics and Geriatric Medicine (Lecture)
- 8) Social Medicine (Lecture)
- 9) Biomedical Ethics II (2 credits, lecture)
- 10) Clinical Ethics (2 credits, lecture)
- 11) Public Health Ethics (2 credits, lecture)
- 12) Global Bioethics (2 credits, lecture)

### Graduate Courses

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

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

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

## Research activities

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

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

#### Specific research topics include:

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

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

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# **Health Sciences and Nursing**

## **2. Preventive and Administrative Nursing**

# Department of Nursing Administration/ Advanced Clinical Nursing

## **Associate Professor**

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

## **Assistant Professor**

Keiko Kunie, Ph.D., R.N.

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

## **Project Assistant Professor**

Ryohei Kida, MSN, R.N.

**Homepage** <http://nurs-adm.umin.jp/>

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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 as the Department of Fundamental Nursing in the School of Health Care and Nursing in 1954. 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, so the department was renamed as Department of Nursing; it was the department responsible for nursing education. In 1992, the School of Health Sciences became the School of Health Sciences and Nursing, two new departments of nursing were established, so the Department of Nursing became once again the Department of Fundamental Nursing. As the result of this shift to the chair of the Graduate School of Medicine in 1996, two departments were established, the Department of Nursing Administration and Department of Advanced Clinical Nursing. Our department is responsible for the fundamental nursing education for undergraduate students.

## **Teaching activities**

### **Undergraduate Courses**

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

#### **Introduction of Nursing Science (1 credit, lectures)**

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, lectures)**

This course provides knowledge and nursing skills for understanding patients and providing care. Students learn about the nursing process and nursing 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, lectures)**

This course offers perspectives on the nursing profession through a series of lectures from various

experts and discussion.

### **Basic nursing skills (2 credits, lectures)**

This course provides the basics for 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 with case discussion.

### **Practicum: basic nursing skills (2 credits, practicum)**

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

### **Nursing Administration (1 credit, lectures)**

This course introduces students to roles of nurse administrators/managers in all types of healthcare settings, such as institutions, organizations, communities, and politics. Students will learn 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 nursing administrative practicum in units or divisions in hospitals. They will learn 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 the lectures and seminar for Nursing Administration and Advance Clinical Nursing.

### **Nursing Administration I, II (2 credits each)**

During this course, students acquire the knowledge and perspectives necessary to become actively involved within an organization and to conduct research that has a focus 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.

### **Advance Clinical Nursing I (2 credits)**

This course offers a critical reading of previous research theories and discussions on 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 methodology that fulfill the organizational and human resource potential to contribute to the wellbeing of patients, nurses, and other health care professions as well as society in general.

### **The Development of Research Methods for Depicting Organizational Phenomena**

The careful extraction and accumulation of knowledge from organizational case studies is necessary to develop nursing administration 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 the dynamic processes of complex workplace-related and organizational processes. For instance, we conduct studies on workplace experiences from studies of multiple organizations as well as describe organizational management processes based on the experiences of those providing support and those receiving the support

### **Discovering Knowledge Required for Effective Organization Management and Organizational Development**

It is important that workers, including nursing administrators, are able to 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 researching nursing organizational operation models during times of crisis based on case studies following the 2011 earthquake and tsunami in Fukushima as well as explaining how nursing managers' competencies and leadership are connected to 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, teams, organizational development, and the improvement of individuals and team environments. Concrete examples include organizational learning, intra-organization communication and roles, and the emotional and psychological development of nursing professionals.

### **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 professionals' expertise, people returning to work in the nursing profession, the functions of hospital departments, and hospital ward construction. During the present academic year, we conducted a survey on the improvement of working hours and environment of nurses for nursing professionals and nursing administrators. This was a Ministry of Health, Labor, and Welfare Policy Research Project.

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# Department of Family Nursing

## Professor

Kiyoko Kamibeppu, Ph.D., R.N., P.H.N., F.A.A.N.

## Lecturer

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

## Assistant Professors

Sachiko Kita, Ph.D., R.N., M.W., P.H.N.

Takafumi Soejima, MHS., R.N., P.H.N.

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

## 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 5 doctoral students, 2 master's students, 33 visiting researchers, and 4 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

1. Kita S, Chan KL, Tobe H, Hayashi M, Umeshita K, Matsunaga M, Uehara N, Kamibeppu K. A follow-up study on the continuity and spillover effects of intimate partner violence during pregnancy on postnatal child abuse. *Journal of Interpersonal Violence*. 2019 Jan; 0886260518821460.
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3. Soejima T, Sato I, Takita J, Koh K, Kaneko T, Inada H, Ozono S, Kamibeppu K. Do childhood cancer and physical late effects increase worries about future employment in adulthood? *Cancer Reports*. 2019 Jun; 2(3): e1175.
4. Tobe H, Sakka M, Kamibeppu K. The efficacy of a resilience-enhancement program for mothers in Japan based on emotion regulation: study protocol for a randomized controlled trial. *BMC Psychology*. 2019 Nov; 7: 69.
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  11. Suzuki S, Oshiro R, Kobayashi A, Kamibeppu K. Nursing support for family decision-making regarding treatment for a neonate with a life-threatening condition. *Journal of Family Nursing*. 2019 Nov; 25(4): 634.

# Department of Community Health Nursing / Public Health Nursing

## **Professor (concurrent)**

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

## **Lecturer**

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

## **Assistant Professor**

Chie Teramoto, Ph.D., R.N., P.H.N.

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

## **Project Assistant Professor**

Chikako Honda, PhD,RN,PHN.

**Homepage** <http://park.itc.u-tokyo.ac.jp/chn/>

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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

## Professor

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

## Assistant Professor (Senior)

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

## Assistant Professor (Junior)

Maiko Noguchi-Watanabe, Ph.D., R.N.

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## Introduction and Organization

The Department of Adult Health Nursing/ Palliative Care Nursing has almost 50 years of history and tradition. Originally the department was started as the *Department of Adult Health* in 1965 and it underwent several re-organizations. The current structure with two sub-divisions of *Adult Health Nursing* and *Palliative Care Nursing* has started in 2006. Further, *Adult Health Nursing* was renamed to *Gerontological Home Care and Long-term Care Nursing* in 2016. Noriko Yamamoto-Mitani has been responsible for administration as a department chair since 2012.

## Education

In the undergraduate program, our department is in charge of the lectures and clinical practicums for *adult health nursing*. In graduate education, we aim to educate students into independent researchers and competent clinicians who effectively use research. For this purpose we respect each student's research interest that they derived from their clinical experiences. Each student completes his/her Master's thesis or doctoral dissertation from developing

research question from their own scientific interests regarding nursing practice for older people or adults in chronic stage.

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

## Research

In research, we aim to contribute to the development of nursing science and improvement in quality of nursing practice through collaborative research with clinicians. Especially we aim to develop new nursing knowledge grounded on Japanese culture, as needed in tomorrow's aged society.

Faculty members conduct studies on various topics in the field of adult and gerontological nursing.

As research methods, along with conventional statistical methods, we often utilize qualitative methods 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' turnover.

We also conduct studies on a range of topics in nursing of chronic conditions, from preventive to end-of-life phase. We have been conducting studies which are expected to allow us to understand the state of individuals who require nursing in those periods, and investigate effective and efficient nursing care for such individuals.

## Publications

1. Sakka M, Goto J, Kita S, Sato I, Soejima T, Kamibeppu K. Associations among behavioral and psychological symptoms of dementia, care burden, and family-to-work conflict of employed family caregivers. *Geriatrics & Gerontology International*. 2019 Jan;19(1):51-55.
2. Matsumoto H, Igarashi A, Suzuki M, Yamamoto-Mitani N. Association between Japanese neighborhood convenience stores and independent living in older people. *Australasian Journal on Ageing* 2019. Jan 30. doi: 10.1111/ajag.12607.
3. Go H, Tanaka M, Yamamoto-Mitani N, Suzuki M, Kawakami A, Masaki N, Shimada M. Medication adherence among patients with chronic hepatitis receiving antiviral treatment. *Gastroenterol Nurs*. 2019 Mar/Apr;42(2):140-149.
4. Noguchi-Watanabe M, Maruyama-Sakurai K, Yamamoto-Mitani N, Matsumoto Y, Yoshie S, Iijima K, Yamanaka T, Akishita M. A community-based program promotes interprofessional collaboration among home healthcare professionals: A non-randomized controlled study. *Geriatrics & Gerontology International*. 2019 Jul; 19(7):660-666.
5. Igarashi A, Matsumoto H, Takaoka M, Kugai H, Suzuki M, Yamamoto-Mitani N. Educational program for promoting collaboration between community care professionals and convenience stores. *Journal of Applied Gerontology*. 2019 Sep 3:733464819871878.
6. Hama T, Takai Y, Noguchi-Watanabe M, Yamahana R, Igarashi A, Yamamoto-Mitani N. Clinical practice and work-related burden among second career nurses: A cross-sectional survey. *J Clin Nurs*. 2019 Sep;28(17-18):3288-3298
7. Futami A, Noguchi-Watanabe M, Mikoshiha N, Yamamoto-Mitani N. Critical thinking disposition among hospital nurses in Japan: Impact of organizational versus personal factors. *Japan Journal of Nursing Science*. 2019 Oct 22:e12298. doi: 10.1111/jjns.12298.
8. Eguchi H, Kachi Y, Koga K H, Sakka M, Tokita M, Shimazu A. Validation of the Japanese version of the multidimensional measure of family supportive supervisor behaviors (FSSB-J). *Front Psychol*. 2019 Nov 22;10:2628.
9. Tobe H, Sakka M, Kamibeppu K. The efficacy of a resilience-enhancement program for mothers in Japan based on emotion regulation: study protocol for a randomized controlled trial. *BMC Psychology*, 2019 Nov 6;7(1):69.
10. Futami A, Noguchi-Watanabe M, Yamamoto-Mitani N. Relationship between critical thinking disposition and use of research-based information among nurses in Japan. *Journal of Japan Academy of Nursing Science*. 2019; 39:261-269.



# Department of Midwifery and Women's Health

## Professor

Megumi Haruna, Ph.D., R.N.M., P.H.N.

## Assistant Professor

Emi Sasagawa, Ph.D., M.P.H., R.N.M.

## Assistant Professor

Kaori Yonezawa, Ph.D., R.N.M., P.H.N.

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

## Introduction and Organization

The Department of Midwifery and Women's Health was established in 2002.

It has 3 faculty members introduced above, 16 graduate students (10 in master's courses, 6 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) Adequate maternal nutrition and weight management  
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. Based on our investigations on the optimal maternal nutritional status and gestational weight gain, we propose a health guidance that can help lower the risk of pregnancy complications and adverse birth outcomes in pregnant women.

- 2) Effect of physical activity during pregnancy  
This study 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.
  - 3) Secondhand smoke exposure during pregnancy and its related factors in Mongolia  
This study uses biomarkers to investigate the prevalence of secondhand smoke (SHS) exposure during pregnancy and the effects of SHS on birth outcomes in Mongolia. Data were collected through investigations to create an effective health education.
  - 4) Factors associated with mental health among working pregnant women  
This study explores factors associated with work engagement among working pregnant women.
2. Development of a support system for reliable childbirth
    - 1) 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.
    - 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 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.

3. Development of a support system for women's health

- 1) Life and sleep among working mothers of infants and toddlers  
This study investigates the cadences of daily life and conditions of sleep such as excessive daytime sleepiness and other related factors among working mothers.
- 2) Support for continuous breastfeeding of working mothers  
This study investigates the factors related to breastfeeding continuation among working mothers.
- 3) Intimate partner violence (IPV) and its related factors  
This study clarifies associations between IPV during pregnancy, mother-to-infant bonding failure, and postnatal depressive symptoms.
- 4) Prevalence of anemia among adult women  
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) Prevalence 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.
- 6) Factors related to postpartum parenting self-efficacy  
This study investigates factors related to maternal parenting self-efficacy (self-esteem) during the postpartum period.
- 7) Prevalence of 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 the pelvic floor muscle training program.

4. 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.

## Publications

1. Haruna M, Matsuzaki M, Ota E, Shiraishi M, Hanada N, Mori R. Guided imagery for treating hypertension in pregnancy. *Cochrane Database Syst Rev.* 2019 Apr 27;4: CD011337
2. Hikita N, Haruna M, Matsuzaki M, Sasagawa E, Murata M, Yura A, Oidovsuren O. Is high maternal body mass index associated with caesarean section delivery in Mongolia? A prospective observational study. *Asian/Pacific Island Nursing Journal.* 2019;4(3).
3. Hikita N, Haruna M, Matsuzaki M, Sasagawa E, Murata M, Yura A, Oidovsuren O. Comparison of Knowledge about smoking and passive smoking and urinary cotinine levels in pregnant women and their partners in Mongolia: A cross-sectional study. *Asian/Pacific Island Nursing Journal.* 2019; 4(1).
4. Yonezawa K, Haruna M. Short-term skin problems in infants aged 0–3 months affect food allergies or atopic dermatitis until 2 years of age, among infants of the general population. *Allergy Asthma Clin Immunol.* 2019;15, 74.
5. Kita S, Haruna M, Matsuzaki M, Kamibeppu K. Does antenatal social support affect the relationships between intimate partner violence during pregnancy and perinatal mental health? *Violence Against Women.* 2019;3:1077801219835 052.
6. Rönnerhag M, Severinsson E, Haruna M, Berggren I. Risk management-evaluation of healthcare professionals' reasoning about and understanding of maternity care. *J Nurs Manag.* 2019;Apr 5.
7. Usui Y, Haruna M, Shimpuku Y. Validity and reliability of the Karitane Parenting Confidence Scale among Japanese mothers. *Nurs Health Sci.* 2019;doi: 10.1111/nhs.12633.
8. Hisa K, Haruna M, Hikita N, Sasagawa E, Yonezawa K, Suto M, Ota E. Prevalence of and factors related to anemia among Japanese adult women: Secondary data analysis using health check-up database. *Sci Rep.* 2019; 19;9(1):17048.
9. Sannomiya M, Sasagawa E, Yonezawa K, Hikita N, Haruna M. The Proportions, regulations, and training plans of male midwives worldwide: A descriptive study of 77 countries. *International Journal of Childbirth.* 2019;9(1):5–18.
10. Kikuchi-Noguchi H, Shiraishi M, Matsuzaki M, Haruna M. Physical activity levels in the second trimester of pregnancy and related demographic factors: A cross-sectional secondary data analysis. *Cogent Medicine.* 2019;6:1704607.
11. Emi S, Megumi H, Kaori Y, Naoko H. From “Care in Normal Birth” to “Intrapartum care for a positive childbirth experience”: How was the WHO guideline on normal birth changed? *Journal of Japan Academy of Midwifery,* 2019; 33(1), 50–60. (in Japanese)

# Department of Psychiatric Nursing

## **Professor**

Norito Kawakami, M.D., Ph.D.

## **Associate Professor**

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## **Project Research Associate**

Akiko Inagaki, R.N., P.H.N., Ph.D.

**Homepage** [http:// plaza.umin.ac.jp/heart/](http://plaza.umin.ac.jp/heart/)

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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, 7 doctoral course students, 5 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.

## Publications

1. Nishi D, Imamura K, Watanabe K, Ishikawa H, Tachimori H, Takeshima T, Kawakami N. Psychological distress with and without a history of depression: Results from the World Mental Health Japan 2nd Survey (WMHJ2). *Journal of Affective Disorders*. 2020 Mar 15;265: 545-551. DOI: 10.1016/j.jad.2019.11.089. Epub 2019 Nov 13.
2. Nishi D, Ishikawa H, Kawakami N. Prevalence of mental disorders and mental health service use in Japan. *Psychiatry and Clinical Neurosciences*. 2019 Aug; 73(8):458-465. DOI: 10.1111/pcn.12894.
3. Fukasawa M, Kawakami N, Umeda M, Akiyama T, Horikoshi N, Yasumura S, Yabe H, Suzuki Y, Bromet EJ. Longitudinal associations of radiation risk perceptions and mental health among non- evacuee residents of Fukushima prefecture seven years after the nuclear power plant disaster. *SSM-Population Health*. 2019 Nov 29;10:100523. DOI: 10.1016/j.ssmph.2019.100523.
4. Yasuma N, Narita Z, Sasaki N, Obikane E, Sekiya J, Inagawa T, Nakajima A, Yamada Y, Yamazaki R, Matsunaga A, Saito T, Watanabe K, Imamura K, Kawakami N, Nishi D. Psychological intervention for universal prevention of antenatal and postnatal depression among pregnant women: protocol for a systematic review and meta-analysis. *Syst Rev*. 2019 Dec 1; 8(1):297. DOI: 10.1186/s13643-019-1238-7.
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7. Kuribayashi K, Imamura K, Watanabe K, Miyamoto Y, Takano A, Sawada U, Sasaki N, Suga M, Sugino A, Hidaka Y, Iida M, Sudo M, Tokita M, Kawakami N. Effects of an internet-based cognitive behavioral therapy (iCBT) intervention on improving depressive symptoms and work-related outcomes among nurses in Japan: a protocol for a randomized controlled trial. *BMC Psychiatry*. 2019 Aug 7;19(1):245. DOI: 10.1186/s12888-019-2221-5.
8. Imamura K, Tsutsumi A, Asai Y, Arima H, Ando E, Inoue A, Inoue R, Iwanaga M, Eguchi H, Otsuka Y, Kobayashi Y, Sakuraya A, Sasaki N, Tsuno K, Hino A, Watanabe K, Shimazu A, Kawakami N. Association between psychosocial factors at work and health outcomes after retirement: a protocol for a systematic review and meta-analysis. *BMJ Open*. 2019 Aug 27;9(8):e030773. DOI: 10.1136/bmjopen-2019-030773.
9. Watanabe K, Imamura K, Inoue A, Otsuka Y, Shimazu A, Eguchi H, Adachi H, Sakuraya A, Kobayashi Y, Arima H, Kawakami N. Measuring eudemonic well-being at work: a validation study for the 24-item The University of Tokyo Occupational Mental Health well-being scale among Japanese workers. *Ind Health*. 2020 Apr 2; 58(2):107-131. DOI: 10.2486/indhealth.2019-0074. Epub 2019 Aug 1.
10. Yasuma N, Watanabe K, Matsunaga A, Nishi D, Kawakami N. Personal values in adolescence and suicidality: a cross-sectional study based on a retrospective recall. *BMC Psychiatry*. 2019 Jul 9;19(1): 214. DOI: 10.1186/s12888-019-2194-4.

11. Komase Y, Watanabe K, Imamura K, Kawakami N. Effects of a newly developed gratitude intervention program on work engagement among Japanese workers: a pre- and post-test study. *Journal of Occupational and Environmental Medicine*. 2019 Sep;61(9):e378-e383. DOI: 10.1097/JOM.0000000000001661.
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14. Yasuma N, Watanabe K, Nishi D, Ishikawa H, Tachimori H, Takeshima T, Umeda M, Sampson L, Galea S, Kawakami N. Urbanization and Internet addiction in a nationally representative sample of adult community residents in Japan: A cross-sectional, multilevel study. *Psychiatry research*. 2019 Mar; 273:699-705. DOI: 10.1016/j.psychres.2019.01.094. Epub 2019 Jan 30.
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16. Chiba R, Umeda M, Goto K, Miyamoto Y, Yamaguchi S. Factors related to recovery knowledge and attitudes among professionals in mental health in Japan. *Japan Journal of Nursing Science*, 2019 Aug 27; e12295. DOI: 10.1111/jjns.12295
17. Nakanishi M, Miyamoto Y, Nakashima T, Shindo Y, & Nishida A. Care preferences of healthy, middle - aged adults in Japan and the USA if they acquired dementia: A cross - sectional observational study. *Geriatrics & Gerontology International*, 2019 Jul 7; 19(8), 829-833. DOI: 10.1111/ggi.13729

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# Department of Gerontological Nursing / Wound Care Management

## **Professor**

Hiromi Sanada, R.N., W.O.C.N., F.A.A.N., Ph.D.

## **Associate Professor**

Gojiro Nakagami, R.N., Ph.D.

## **Associate**

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## **Project Research Associate**

Kenneth Scott Barton, M.A.

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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 hospital relating to pressure ulcers 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 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, two part-time lecturers for undergraduate courses, and seven part-time

lecturers for graduate courses. The student body consists of eight doctoral course students, ten 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 Practice (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 practice 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 2019, our program included themes related to:

- a) Policy creation for solving problems confronted in nursing
- b) Health support services
- c) Nursing-based hospital management
- d) Development of medical devices for supporting patients' lives.

#### 2) Overview of Clinical Medicine (S2 in 3rd yr; 2 credits)

The aim of this series of lectures is to learn the basic knowledge and thought process for understanding clinical medicine, and to learn the pharmaceuticals required for nursing practice. The main content themes in the 2019 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 2019 curriculum included:

- a) Introduction to anatomical pathology
- b) Case study
- c) Introduction to anatomicopathological research
- d) Approaches to anatomical pathology
- e) Autopsy room practice
- f) Medical specimen room visit

### 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 2019 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 ulcer, incontinence, support for walking and movement)
- 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) Relationship-building and communication skills with the elderly
- l) Group work

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. Our 2019 program included the following:

- a) Necessity and importance of Nursing Science and Engineering
- b) Methods and application of the research of Nursing Science and Engineering

### **6) Clinical Practice in Gerontological Nursing (A1 in 4th yr; 2 credits)**

The aim of this practicum is to learn about the current state of gerontological nursing through practice (or practical training) in a long-term care facility. The program in 2019 was supported by the long-term care facility owned by Medical Corporation Tatsuoka.

### **7) Bachelor's thesis**

The following research themes were submitted in 2019:

- “New methods for the estimation of weight and body composition of wheelchair users, validated with able-bodied subjects” (in Japanese)
- “Association between wound temperature distribution obtained with a thermography and healing process in pressure ulcer” (in Japanese)

## **2. Graduate course**

### **1) Gerontological Nursing I (S1; 2 credits)**

The main theme of Gerontological Nursing I in 2019 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 2019 were as follows:

- a) Up-to-date ultrasonographic examination and hands-on lecture of ultrasonography for the head and neck area
- b) Dysphagia
- c) Biochemistry of wound healing, protein synthesis, and nutritional management in cancer patients
- d) How do cells sense stress?
- e) Activities of perianesthesia nurses and research on skin
- f) How can we approach aging and skin health?
- g) Innovations in basic nursing education: on moving from ‘home care nursing’ to ‘community and home care nursing’

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

The main topic of Wound Care Management I in 2019 was the acquisition of the basic knowledge (i.e., basic biology, clinical research, and engineering) necessary to understand wound management studies. The topics were as follows:

- a) Structure and function of skin; wound healing and management
- b) Basics of biological research and its application to wound care nursing
- c) Basics of engineering research and its application to wound care nursing
- d) Basics of ultrasound technology and its application to wound care nursing
- e) Basics of pressure ulcer and efforts of nursing

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

The main theme of Wound Care Management II in 2019 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 2019:

- “Reliability and validity of skin blotting examination for non-invasive assessment of the physiological status of the skin”
- “Developing a pressure ulcer monitoring tool using electrical impedance tomography and spectroscopy: Phantom study and preliminary human trial”
- “Incidence, characteristics and timing of peripheral intravenous catheter failure in patients receiving chemotherapy with hematological malignancy; a prospective descriptive study”
- “Polymorphism analysis of candidate risk genes for pressure ulcers in older Japanese patients: A cross-sectional study at a long-term care hospital”
- “Skin characteristics associated with foot callus in people with diabetes: A cross-sectional study focused on adhesion molecules in corneocytes”

## Research activities

### 1. Activity policy

Our gerontological nursing research focuses on those suffering from geriatric syndromes, such as pressure ulcers, incontinence, malnutrition, pain, dysphagia, osteoporosis and dementia. Our wound care management research focuses on pressure ulcers, diabetic foot ulcers, 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. We also attend the Foot Care Outpatient Clinic held by the Department of Metabolic Diseases and the Stoma Outpatient Clinic held by the Departments of Urology and Colorectal Surgery.

In July 2019, we organized the 6th introductory seminar for bioengineering nursing research involving many nursing researchers and clinical nurses. In this seminar, a new research framework “Bioengineering Nursing” which consists 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. Furthermore, we organized an advanced hands-on seminar of bioengineering nursing research methodologies for those who attended the introductory seminar and were interested in this research framework.

Regarding international activities, we attended the International summer school in Nottingham Trent University in September 2019. Researchers from several countries discussed chronic wounds, skincare, and lymphoedema. Additionally, 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 The University of Nottingham (UK). Professor Sanada has been working as Continental Board for World Union of Wound Healing Societies and a member of the International Board of Directors for International Lymphoedema Framework. Her research activities on the globalization of interdisciplinary research have been highly evaluated, and she was recommended as a Fellow of American Academy of Nursing (FAAN).

### 2. Research fields and themes in 2019

#### 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
- Research on the mechanisms of wound pain

#### 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 ulcers
  - 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 of latent dysphagia
  - Establishment of a novel assessment method of 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
- Several awards were given for our research, as follows:
- The 8th Asia Pacific Enterostomal Therapy Nurse Association Best Oral Award  
Nakagami G, Sanada H, Mori Y, Minematsu T, Kitamura A. Biofilm-based wound care system for treating chronic wounds. 2019. (The 8th Asia Pacific Enterostomal Therapy Nurse Association, Taipei International Convention Center, Taipei, Taiwan, 22nd Nov)
  - The 8th Asia Pacific Enterostomal Therapy Nurse Association Best Moderated Poster Award  
Nakai A, Tsukatani T, Tamai N, Urai T, Mori Y, Weijie K, Minematsu T, Takada C, Sanada H. Relationship between type IV collagen positivity via skin blotting and conventional risk factors of skin tears. 2019. (The 8th Asia Pacific Enterostomal Therapy Nurse Association, Taipei International Convention Center, Taipei, Taiwan, 22nd Nov)
  - The 8th Asia Pacific Enterostomal Therapy Nurse Association Best Moderated Poster Award  
Minematsu T, Tsukatani T, Weijie K, Nakai A, Tomida S, Nakagami G, Sanada H. Intra-rater reliability of albumin measurement by skin blotting in healthy volunteers. 2019. (The 8th Asia Pacific Enterostomal Therapy Nurse Association, Taipei International Convention Center, Taipei, Taiwan, 22nd Nov)
  - First-place award from the 21st Japanese Society of Pressure Ulcers Board Meeting.  
Maeda T, Tamai N, Minematsu T, Noguchi H, Nakagami G, Yabunaka K, Sanada H. Relationship between pressure ulcers and dynamic buttock pressure distributions during performance in wheelchair basketball athletes. *Journal of Japanese Society of Pressure Ulcers*. 2019;21(3):309. (The 21st Japanese Society of Pressure Ulcers Board Meeting, Kyoto, 23rd Aug)
  - Award from the 28th Annual Congress of Japanese Society of Wound, Ostomy, and Continence Management.  
Minematsu T, Ogata M, Tamai N, Yabunaka K, Maeda T, Nakagami G, Noguchi H, Sanada H. Deep tissue injury in wheelchair basketball athletes: skin characteristics related to deep tissue injury. *Journal of Japanese Society of Wound, Ostomy and Continence Management*. 2019;23(2):242. (The 28th Annual Congress of Japanese Society of Wound, Ostomy, and Continence Management, Nara, 25th May)
  - Good design award 2019  
Dai M, Batelplus Inc, Yoshida Tsukasa Inc, Murayama, Murayama H. Elastic Stockings for Patients with Lymphedema "Cool lala"

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2. Suzuki M, Miyazaki H, Kamei J, Yoshida M, Taniguchi T, Nishimura K, Igawa Y, Sanada H, Homma Y. Ultrasound-assisted prompted voiding care for managing urinary incontinence in nursing homes: A randomized clinical trial. *Neurourology Urodynamics*. 2019;38(2):757-63.
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4. Higuchi S, Yoshida S, Minematsu T, Ichinose T. Detection of inflammatory cytokines by skin blotting as an objective measure of neonatal skin problems. *Journal of Nursing Science and Engineering*. 2019;6(1):33-40. [doi]
5. Matsumoto M, Yabunaka K, Yoshida M, Nakagami G, Sanada H. Validity assessment of two bladder volume estimation methods using hand-held ultrasonography devices: verification with a small amount of bladder urine. *Journal of Nursing Science and Engineering*. 2019;6(1):22-32.
6. Kunimitsu M, Nakagami G, Kitamura A, Mugita Y, Akamata K, Sasaki S, Hayashi C, Mori Y, Sanada H. The combination of high bacterial count and positive biofilm formation is associated with the inflammation of pressure ulcers. *Chronic Wound Care Management and Research*. 2019;6:1-7.
7. Nakai A, Minematsu T, Tamai N, Sugama J, Urai T, Sanada H. Prediction of healing in category I pressure ulcers by skin blotting with plasminogen activator inhibitor 1, interleukin-1 $\alpha$ , vascular endothelial growth factor C, and heat shock protein 90 $\alpha$ : A pilot study. *Journal of Tissue Viability*. 2019;28(2):87-93.
8. Takehara K, Oe M, Ohashi Y, Tsunemi Y, Kadowaki T, Sanada H. Differences between subjective and objective symptoms of the foot in patients with diabetes. *Journal of Wound, Ostomy and Continence Nursing*. 2019;46(2):113-6.
9. Kumagai A, Ohno N, Miyati T, Okuwa M, Nakatani T, Sanada H, Sugama J. Investigation of effects of urethane foam mattress hardness on skin and soft tissue deformation in the prone position using magnetic resonance imaging. *Journal of Tissue Viability*. 2019;28(1):14-20.
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- wound model in rats. *Experimental Dermatology*. 2019.;28(9):1010-6.
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  21. Okawa Y, Fukudo S, Sanada H. Specific foods can reduce symptoms of irritable bowel syndrome and functional constipation: a review. *BioPsychoSocial Medicine*. 2019;13:10.
  22. Abe-Doi M, Murayama R, Yabunaka K, Tanabe H, Komiyama C, Sanada H. Ultrasonographic assessment of an induration caused by extravasation of a non-vesicant anti-cancer drug: A case report. *Medicine*. 2019;98(14):e15043.
  23. Astrada A, Nakagami G, Suriadi, Sanada H. Successful wound treatment of a diabetic foot ulcer exposing bone with Trigona honey: a case study. *Journal of Wound Care*. 2019;28(Sup12):S4-S8.
  24. Noguchi H, Koyano Y, Mori H, Komiyama C, Sanada H, Mori T. Exploration of communication robot use for older patients in an acute hospital based on case trials. *Journal of Nursing Science and Engineering*. 2019;6(2):70-82.
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# **International Health**

## **1. International Social Medicine**

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# 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 2020 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; 14 doctoral students; and eight 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 2018:

- Innovations in global health
- Global health policy
- Global health governance
- Social determinants of health
- Universal health coverage
- Global health diplomacy
- Quantifying health outcomes
- Using GBD to inform policies
- Old and new challenges in global health
- Comparative risk assessment
- Health system performance assessment
- Health service quality
- Monitoring and evaluation
- Financing health systems

### **GHP Monday seminar**

Every Monday, 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**

A comprehensive study on the comparative risk assessment and utilization of health outcomes by prefecture in Japan. Grant-in-Aid for Scientific Research(C) (Ministry of Education, Culture, Sports,

Science and Technology). PI: Shuhei Nomura

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

Research on cancer risk assessment and prevention guideline recommendations through active utilization of the research collaboration infrastructure in Japan and overseas. (National Cancer Center Research and Development Fund). 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

The role of the private health sector in UHC: challenges and opportunities in Asia,(World Health Organization). PI: Kenji Shibuya

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

Development of health system performance evaluation methods by prefecture in Japan. Research on Region



Medical (Ministry of Health, Labour and Welfare). PI: Kenji Shibuya

Development and research of strategic and effective interventions in the field of international health in Japan, based on the analysis of international health policies in each country. Research on Policies for Global Health Issues (Ministry of Health, Labour and Welfare). PI: Kenji Shibuya

## Selected Publications

1. Yoneoka D, Nomura S, Kurotani K, Tanaka S, Nakamura K, Uneyama H, Hayashi N, Shibuya K. Does Japan's national nutrient-based dietary guideline improve lifestyle-related disease outcomes? A retrospective observational cross-sectional study. *PLoS ONE*. 2019; 14(10): e0224042.
2. Khaing HT, Nomura S, Yoneoka D, Ueda P, Shibuya K. Risk factors and regional variations of malnutrition among children under 5 in Myanmar: cross-sectional analyses at national and subnational levels. *BMJ Open*. 2019;9:e030894.
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4. Hasegawa M, Murakami M, Nomura S, Takebayashi Y, Tsubokura M. Worsening Health Status among Evacuees: Analysis of Medical Expenditures after the 2011 Great East Japan Earthquake and Nuclear Disaster in Fukushima. *Tohoku J. Exp. Med*. 2019, 248, 115-123
5. Nomura S, Matsuzaki Y, Sato Y, Takasaki J, Sonoda Y, Shimmura H, Kodama Y. A Comparative Survival Analysis Between Evacuees and Nonevacuees Among Dialysis Patients in Fukushima Prefecture After Japan's 2011 Fukushima Nuclear Incident. *Disaster Med Public Health Prep*. 2019;1-7.
6. Zhang C, Rahman MS, Rahman MM, Yawson AE, , Shibuya K. Trends and projections of universal health coverage indicators in Ghana, 1995-2030: a national and subnational study. *PLoS ONE*. 2019; 14(5): e0209126.
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8. Yang JJ, Yu D, Wen W, Saito E, Rahman MS, Shu XO et al. Association of diabetes with all-cause and cause-specific mortality in Asia: a pooled analysis of more than 1 million participants. *JAMA Netw Open*. 2019;2(4):e192696.
9. Ghaznavi C, Sakamoto H, Yoneka D, Nomura S, Shibuya K, Ueda P. Trends in heterosexual inexperience among young adults in Japan: analysis of national surveys, 1987 - 2015. *BMC Public Health*. 2019; 19:355.
10. Yang JJ, Yu D, Wen W, Shu XO, Saito E, Rahman MS, Gupta et al. Tobacco Smoking and Mortality in Asia: A Pooled Meta-analysis. *JAMA Network Open*. 2019; 2(3), e191474-e191474.
11. Amimo F, Moon TD, Magit A, Sacarlal J, Lambert B, Nomura S. Trends in comparative efficacy and safety of malaria control interventions for maternal and child health outcomes in Africa: a study protocol for a Bayesian network meta-regression exploring the effect of HIV and malaria endemicity spectrum. *BMJ Open*. 2019; 9(2): e024313.
12. Nishikawa Y, Tsubokura M, Takahashi Y, Nomura S, Ozaki A, Kimura Y, Morita T, Sawano T, Oikawa T, Nakayama T. Change of access to emergency care in a repopulated village after the 2011 Fukushima nuclear disaster: a retrospective observational study. *BMJ Open*. 2019; 9(2): e023836.
13. Tanaka S, Sawada N, Yamaji T, Goto A, Iwasaki M, Inoue M, Tsugane S. Female reproductive factors and risk of lymphoid neoplasm: The Japan Public Health Center - based Prospective Study. *Cancer Science*. 2019. Online first.
14. Sakamoto H, Lee S, Ishizuka A, Hinoshita E, Hori H, Ishibashi N, Komada K, Norizuki M, Katsuma Y, Akashi H, Shibuya K. Challenges and opportunities for eliminating tuberculosis - leveraging political momentum of the UN high-level meeting on tuberculosis. *BMC Public Health*. 2019;19:76.

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# Department of Community and Global Health

## Professor, Academic Leader

Masamine Jimba, MD, PhD, MPH

## Assistant Professors

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## 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 April 2019, the members of the department include the department chair and professor, 3 assistant professors, 3 secretaries, 12 visiting lecturers, 19 doctoral students, 19 master's degree students, and 38 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 China through Parent and Child Health Handbook Promotion Association of Japan. 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. In addition, as the President of Asia-Pacific Academic Consortium for Public Health, Professor Jimba takes 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. Miller R, Tomita Y, Ong KIC, Shibanuma A, Jimba M. Mental well-being of international migrants to Japan: a systematic review. *BMJ Open*. 2019 Nov 3;9(11):e029988.
2. Carandang RR, Shibanuma A, Kiriya J, Vardeleon KR, Marges MA, Asis E, Murayama H, Jimba M. Leadership and Peer Counseling Program: Evaluation of Training and Its Impact on Filipino Senior Peer Counselors. *Int J Environ Res Public Health*. 2019 Oct 24;16(21).
3. Okitsu S, Khamrin P, Takanashi S, Thongprachum A, Hoque SA, Takeuchi H, Khan MA, Hasan SMT, Iwata T, Shimizu H, Jimba M, Hayakawa S, Maneekarn N, Ushijima H. Molecular detection of enteric viruses in the stool samples of children without diarrhea in Bangladesh. *Infect Genet Evol*. 2019 Oct 17;77:104055.
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# **International Health**

## **2. International Biomedical Sciences**

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# 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.

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

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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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# Department of Developmental Medical Sciences

## Professor

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## Research Associate

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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

## Professor

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## Research Associates

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## Introduction and Organization

The Department of Human Ecology was founded when Kenji Uruguchi was appointed to the professorship of the Human Ecology Department on April 1, 1965. Following the retirement of Professor Uruguchi 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 2019, 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.

## 3. Nutrition and eating behaviors in Indonesia

We have been conducting field surveys every year in the same villages in West Java, Indonesia. In 2019, we conducted an interview survey with a questionnaire on food insecurity, as well as updated the basic information of the households in the village. In addition, we obtained the growth records of children and analyzed them.

## 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.

## 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.

## 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

## Professor

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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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# Department of Social and Preventive Epidemiology

## Professor

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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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# Department of Clinical Epidemiology and Health Economics

## Professor

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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.

The Department accepted 12 master students for the fiscal years of 2019.

## 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

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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. Interpersonal communication skills for behavioral changes
4. Public health communication skills for behavioral changes
5. Communicating for policy and advocacy
6. Communication in group and organization
7. Patient and public education
8. Communication with foreign patients
9. Entertainment education
10. Visual communication
11. Media and communication (1): Television
12. Media and communication (2): News paper
13. Media and communication (3): Internet
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 CDISC standards
2. Introduction to data management in clinical

research

3. Data and metadata – Define.xml
4. Standardization of case report form – CDASH
5. Standardization of data format – SDTM
6. Standardization of dataset for analysis – AdaM
7. Electronic application by CDISC standards

In the undergraduate program, we present lectures entitled “Medical Literature Informatics” and “health communication.”

## Research Activities

The followings are two distinguishing characteristics of the research conducted in our Department of Health Communication, as compared to the research at other medical informatics programs in Japan:

(1) 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.

(2) 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.

The following are current research topics at the Department of Health Communication:

(1) 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.”

(2) 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.

(3) 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.

(4) 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 presents challenges. We also conduct researches to increase influence of small media such as leaflets, and held seminars for health professionals.

(5) Research Related to UMIN Activities

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.

(6) 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.

(7) 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.

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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.

## **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.

## 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.

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. 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 will be conducted in 2018.

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.

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# **School of Public Health**

## **3. Health Services Sciences**

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# Department of Clinical Information Engineering

## Professor

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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

## Teaching activities

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.

In this year, we also provided a special lecture entitled “Air pollution, climate change and human health” to

undergraduate students from three schools (Peking University, Seoul National University, and The University of Tokyo) in the 2019 CAMPUS Asia Summer Program, hosted by East Asian Academy for New Liberal Arts (EAA), The University of Tokyo.

## 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

## Research activities

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

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# **Endowed Department**

# Department of Artificial Intelligence in Healthcare

## **Project Associate Professor**

Yoshimasa Kawazoe, M.D., Ph.D.

## **Project Research Associate**

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## **Introduction and Organization**

The transformation of industrial structures has become inevitable in many fields with the arrival of the practical application of artificial intelligence (AI). Healthcare is not exempt from this trend, and the development of services based on AI and information and communications technology (ICT) are anticipated. The present program was inaugurated in August 2018 sponsored by the Hanshin Dispensing Holding Co., Ltd. and Em Systems Co., Ltd. and with the cooperation of the Department of Biomedical Informatics, Division of Social Medicine, Graduate School of Medicine, The University of Tokyo, which has been involved in the development of hospital data systems and standardization of medical data, and the Department of Healthcare Information Management of The University of Tokyo Hospital. At the time of its inauguration, the activities of the program consisted of 1) defining the form of new medical services utilizing AI and ICT, 2) developing the technological groundwork and 3) establishing a center to provide support for researchers involved in the project, thereby 4) educating and training competent candidates in this field.

## **Teaching activities**

We are promoting activities to cultivate researchers in this field by educating and training internal and external graduate students. In 2018, we advised doctorate students in the joint program, the Department of Biomedical Informatics, and offered courses for the School of Public Health (SPH). In 2019, we plan to accept graduate students from other programs and students from other universities for practical training, and we also hope to improve the AI and IT skills of hospital staff by hosting internal seminars.

## **Research activities**

In the present program, we seek to apply data primarily obtained from electronic medical records using information processing technology and machine learning technology to develop technologies that assist diagnosis. The main research themes of the present program are listed below.

1. Development of information extraction and processing infrastructure from medical records

It is difficult even to determine which disease a patient is receiving treatment for by computer

processing alone based on records in the current electronic medical record system. For example, disease names inputted for the purpose of health insurance claims do not reflect actual disease names. There are also only few diseases that can be determined based on medication or biopsy testing results. Therefore, it is anticipated that the utilization of natural language processing technology will make it possible to extract data from records of treatment and test reports. Examples may include basic tasks, such as creating written summaries based on a patient's symptomatic and clinical data, to more complex tasks, such as discovery of new clinical knowledge. To date, we have developed a term database to provide solutions for non-standardized terms and abbreviations of symptoms and disease nomenclature characteristic of medical documents, funded by the Ministry of Health, Labour and Welfare (MHLF) Grants-in-Aid for Scientific Research (Kakenhi) in a joint research with the MEDNLP (Manbyo Dictionary) of the Nara Institute of Science and Technology. We are also developing a method of obtaining the semantic representation of a text by extracting terms constituting the text and mapping them onto concepts defined by clinical ontology and repeated synthesis of adjacent concepts. This process allows "reading between the lines" to infer other concepts based on explicitly written concepts.

## 2. Automatic diagnostic classifications based on histopathological images of kidney disease

The widespread use of AI technology has seen an unprecedented advancement in automation of diagnostic classification based on medical images. The present program is funded by the MHLW Kakenhi and seeks to build a database of pathology images of kidney disease biopsies in a multicenter joint research. It has also been working on developing methods of diagnoses on glomerular histological images applying Convolutional Neural Networks (CNN). Our achievements to date are summarized as follows.

1) A facility participating in the study built a database based on the 112,210 fluorescent antibody images and 7,123 Whole Slide Image (WSI) that were provided to it. 2) A CNN assessment of estimated accuracy of

fluorescence intensity in images of glomeruli stained by IgG fluorescent antibodies (F1) showed fluorescence intensity in the mesangial, loop wall, and other regions were 75.6%, 67.9% and 60.5%, respectively. 3) A method using Faster R-CNN on pathologic optic microscopy images to detect microscopic glomeruli from high-resolution WSI was developed, achieving a higher detection accuracy than previous studies. 4) Twelve items in findings in PAS staining were identified through discussion between the five study group member experts in renal pathology. Assessment of the degree of coincidence indicated that there was a spread between the findings, with kappa indices of 0.04 - 0.43. 5) The accuracy according to CNN, which classifies glomerular findings based on one glomerular image, resulted in a ROC-AUC exceeding 0.9 for Extracellular matrix sclerosis / Collapsing obsolete and Crescent. The focal points of the CNN were also visualized to analyze errors in the analysis. 6) The outcomes of this study were applied to the development of a WEB application system that detects the glomerular region from WSI. We plan to publish the results as a dataset with annotations in the future.

## 3. Prediction of clinical events from composite chronological medical data

AI for medical images and videos have been developed for each imaging modality, and practical implementation is likely to happen soon. Meanwhile, there is also a flourishing body of research on models applying data other than images, such as electronic medical records including medication and testing result data to predict clinical events. Electronic medical records contain a lot of longitudinal data; that is, data on one subject that is followed up and collected over multiple points in time. However, this makes it difficult to develop prediction models. For example, results of sampling tests such as blood and urine test are typical types of longitudinal data. They are also chronological data on multiple variables considering the many parameters examined in sampling tests. However, not all parameters are measured at the same time, and they are also taken at irregular intervals, which means that missing values make it difficult to be handled as chronological data

and cause problems when attempting to analyze them. Similar problems also occur in using data collected from sources other than sampling test results, such as medication orders and disease names entered for insurance purposes. The present program aims to develop methods that apply multiple types of medical data as chronological order. In the past, we have reported the application of a method using convolutional encoder for interpolation of missing data from blood tests that are taken at irregular intervals for higher accuracy of data compared to linear interpolation. In another study, we reported on the efficacy of a neural network model that classifies prognosis based on low level feature values extracted with an anti-encoder that accounts for missing values from a series of diabetes test items.

4. Research and development of a hospital data system for cancer genetic panel testing

With the budding application of clinical genome sequencing, the genetic panel testing *TodaiOncoPanel* project was established in Tokyo University Hospital in 2018 under the field of advanced medical care. In 2019, genetic panel testing *NCC OncoPanel*, *F1CDX* was started as part of insured health service. What is notable among these cancer genomic panel studies is that the three parties: the core and cooperative hospitals, the Center for Cancer Genomics and Advanced Therapeutics (C-CAT) and testing companies are connected by a network to send clinical data and genomic sequencing data collected throughout the nation to C-CAT. Program chairman Kawazoe has been a member of the Working group for the Core Hospitals and Cooperative Hospitals for Cancer Genomic Medicine and has been conducting research on information related to the applications of genomic data through developing an information system for genomic medicine. We are also collaborating with the Department of Genomic Medicine in The Tokyo University Hospital to improve in-hospital application systems.

## Social activities

1. We have clarified the challenges for applying AI in health care by giving presentations at various conferences.

2. Appointed a member of the Japanese Medical Association *Gakujutsu suishinkaigi* (Academic Promotion Committee), we have been involved in defining the status quo and establishing the challenges in AI application in health care.
3. Member of the *ICD10 Hyoujun byoumei masuta kentou iinkai sagyohan* [Working Group to the Master Committee of Standard Disease Nomenclature: 10th revision of the International Statistical Classification of Diseases and Related Health Problems]: Promoting standardization of disease names and relevant codes on the electronic medical record system as well as the consistent and widespread use of such names and codes.

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# Health Economy and Society Policy

## Project Professor

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## Introduction and Organization

Health Economy and Society policy is a donated fund course established in 22<sup>nd</sup> 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. We also promote manpower training programs (Program for "The movements of medical value") in health technology assessment with collaboration departments.

## 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 on the disease burden in Japan.
- 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) that makes use of big data. 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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# Department of medical research and the management of musculoskeletal pain

## **Professor**

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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 Nippon Zoki Pharmaceutical, AYUMI Pharmaceutical, Ono Pharmaceutical, Sampo Holdings, Inc., NuVasive Japan, Inc, Promotion of Practical Use of AI Medical Diagnosis Support Equipment, MTG Co., Ltd., Shionogi & Co., Ltd. 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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# Department of Medical Genomics

## **Project Associate Professor**

Noriko Hosoya, M.D., Ph.D. (~April, 2019).

## **Project Assistant Professor**

Satoshi Inoue, Ph.D.

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## **Introduction and organization**

Department of Medical Genomics was established with Project Professor Hiroyuki Mano in September 2009 with the goal to identify essential growth drivers in every cancer, by taking advantage of our functional screening system coupled with the next generation sequencing technologies. Department of Medical Genomics had been settled by the tight support from Department of Molecular Pathology (Professor Kohei Miyazono) and by the donation from Astellas Pharma Inc. and Illumina, Inc. Starting as of September 2012, Department of Medical Genomics had been run only by the donation from Astellas Pharma Inc. In April 2013, Project Professor Hiroyuki Mano was promoted to be the Professor of Department of Cellular Signaling which then co-supported this department. Instead, Project Associate Professor Yoshihiro Yamashita led this department. Starting from September 2014, Department of Medical Genomics has entered the second 5-year term by the support from Eisai Co., Ltd. In September 2014, Dr. Yoshihiro Yamashita was promoted to become Associate Professor at Department of Cellular Signaling, and this department was run by the leadership of Project Associate Professor Eirin Sai. After the retirement of Dr. Sai in March 2017, Dr. Masahito Kawazu managed this department as Project Associate Professor from April 2017 until March 2018. From April 2018, Dr. Shogo Ehata took his position as Project Associate Professor of this department until August 2018, and was then promoted to become Associate Professor of Environmental Science Center of The University of Tokyo. From September 2018, this department has been co-supported by Laboratory

of Molecular Radiology (Professor Kiyoshi Miyagawa). From November 2018, Dr. Noriko Hosoya served as Project Associate Professor of this department until April 2019, and then was promoted to become Associate Professor of Laboratory of Molecular Radiology in May 2019.

Department of Medical Genomics enjoyed a wide range of research collaboration with many academic institutes within Japan and also from abroad. Especially, this department was under an intimate collaboration with Department of Molecular Pathology and Laboratory of Molecular Radiology. We also supported cancer genomic medicine using a multiplex genome sequencing, named "Todai OncoPanel" at the University of Tokyo Hospital. This department ended in August 2019.

## **Teaching activities**

We took the responsibility for the lectures of general pathology and basic radiation medicine as well as the training of handling radioactive materials for the undergraduate students of School of Medicine. We also accepted undergraduate students taking "Free Quarter" and "Early-Exposure-to-Medicine" courses. We also took part in the education of radiation health science for the 3rd year students of School of Integrated Health Sciences and the lectures of molecular biology for graduate students of the Graduate School of Medicine. We also delivered training on basic medical research for both undergraduate students and graduate students.

## Research activities

Department of Medical Genomics tried to fulfill our goals mainly through the following approaches.

(1) Functional screening with the use of retroviral cDNA expression libraries.

The focus formation assay had been widely used in 1980s and 1990s to identify oncogenes from human cancer. However, since this technology directly uses cancer genome to transfer oncogenes into recipient cells, expression of each gene is regulated by its own promoter/enhancer fragments. Therefore, such technology is theoretically unable to capture oncogenes whose promoter/enhancer is silent in recipient cells. To make every gene expressed sufficiently in recipient cells, we here developed a highly efficient retrovirus-mediated cDNA expression library system. Our system enables to make a library with high complexity (containing millions of independent cDNA clones) even from  $< 10^4$  of cells.

Application of this technology to a lung cancer specimen led to the discovery of a novel fusion-type oncogene *EML4-ALK* (*Nature* 448:561). A tiny chromosomal inversion, inv(2)(p21p23), within lung cancer cells fuses *EML4* (Echinoderm microtubule associated protein like 4) to *ALK* (anaplastic lymphoma kinase), resulting in the production of a constitutively active tyrosine kinase EML4-ALK.

Many pharmaceutical companies are currently developing ALK inhibitors, and more than six of different inhibitors are under clinical trials to treat EML4-ALK-positive lung cancer. The efficacy of one of such compounds, crizotinib, has been published already, and, surprisingly treatment with crizotinib resulted in ~90% of response rate plus the presence of patients under complete remission. Crizotinib was approved as a therapeutic drug against lung cancer as of August 2011, which is the record-breaking speed in the history of cancer drug development.

We examined gene copy number of *EML4-ALK*-positive tumors in a genome-wide manner, and found that copy number alterations in oncogenes and tumor-suppressor genes are significantly less frequent in tumors harboring *EML4-ALK* than those without it.

(2) Cancer genome resequencing

In addition to the functional screening shown above, we also tried to search for somatically mutated genes

in human cancers with the use of “the next generation sequencers (NGS)”. While development of NGS has enabled us to determine the full genome sequence of a cancer specimen even in private laboratories, it is still a demanding task to conduct full-genome sequencing for a large number of samples. Therefore, many laboratories now purify exonic fragments from a sample genome, and determine their sequences. However, since gene fusions usually take place at intronic regions, such sequencing approach with captured exons fails to discover fusion genes.

Thus, we have developed a “cDNA-capture system”, in which exon capture is conducted on cDNA, not genomic DNA. With this technology, a single NGS experiment can detect point mutations, insertions/deletions and gene fusions simultaneously (*Cancer Sci* 103:131)

We applied this technology to a human fibrosarcoma cell line, HT1080, leading to the discovery of oncogenic mutants among small GTPases, NRAS(Q61K) and RAC1(N92I) (*PNAS* 110:3029). Interestingly, RAC1(N92I), but not NRAS(Q61K), was shown to be an essential growth driver to which cancer cells are addicted.

(3) High-throughput functional evaluation method

Numerous variants of unknown significance (VUS) have been identified through large-scale cancer genome projects, although their functional relevance remains uninvestigated. The L858R substitution or exon 19 deletions are, for instance, known to confer activation of epidermal growth factor receptor (EGFR) kinase, but there are more than one thousand of nonsynonymous mutations within *EGFR* reported in the COSMIC database. It is still obscure whether such mutations have some relevance to EGFR kinase activity or are merely passenger mutations. To drastically increase the speed of functional annotation, here we have developed a mixed-all-nominated-mutants-in-one (MANO) method to evaluate the transforming potential and drug sensitivity of oncogene VUS in a high-throughput manner. To validate its usefulness, we applied this method to 101 nonsynonymous *EGFR* mutants, and successfully evaluated clinical relevance of each mutations. Also, we assessed functional relevance of 55 VUSs in the ERBB2 gene, revealing that many VUSs have distinct sensitivity to different ERBB2 inhibitors.

#### (4) Comparative analysis of TTF-1-binding DNA regions in SCLC and non-SCLC

In collaboration with a group at the Department of Molecular Pathology, we have conducted genome-wide comparative analysis of thyroid transcription factor-1 (TTF-1, encoded by the *NKX2-1* gene)-binding DNA regions in small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC). TTF-1 is highly expressed in both SCLC and NSCLC. TTF-1 antagonizes the effect of TGF- $\beta$  in the induction of epithelial-mesenchymal transition (EMT) in NSCLC, and functions as an anti-tumorigenic factor. We compared the genome-wide distributions of TTF-1 binding regions and the transcriptional programs regulated by TTF-1 using a human SCLC cell line NCI-H209 (H209) and a human lung adenocarcinoma (NSCLC) cell line NCI-H441 (H441), by ChIP-seq and RNA-seq analyses. TTF-1 binding regions in H209 and H441 cells differed by 75.0%. ASCL1 (also known as ASH1) is an E-box binding basic helix-loop-helix transcription factor, and a lineage-survival oncogene of SCLC. We found that TTF-1 and ASCL1 were coexpressed and bound to adjacent sites on target genes in SCLC, and cooperatively regulate transcription of them. Moreover, TTF-1 regulated expression of the Bcl-2 gene family and showed anti-apoptotic function in SCLC. Thus, TTF-1 promotes SCLC growth by partly coordinating with ASCL1 and serves as a pro-tumorigenic factor in SCLC (also see the Section of “Department of Molecular Pathology”).

#### (5) Molecular mechanisms underlying DNA repair and its regulation

Genomic instability describes a state in which there is an increased tendency to acquire genetic alterations and is a hallmark of cancer. Aberrations in DNA repair machinery in cancer cells not only cause genomic instability but also provide promising biomarkers or targets for cancer therapy. While both activation and inactivation of DNA repair are observed in various sporadic cancers, the molecular mechanisms underlying aberrations in DNA repair machinery are not fully understood. We recently focus on the roles of “cancer-testis antigens”, which are normally expressed only in the germ cells but are also expressed at varying levels in cancer. We have reported that these antigens can modulate DNA repair in cancer in various manners. For example, the cancer-testis

antigen SYCP3 impairs mitotic DNA double-strand break repair by interfering with the homologous recombination protein BRCA2 (Hosoya et al, *EMBO Rep* 2012). Another cancer-testis antigen SYCE2 constitutively insulates the chromatin-related protein HP1 $\alpha$  from heterochromatin and potentiates DNA double-strand break repair, inducing radioresistance (Hosoya et al, *Life Science Alliance* 2018). Based on these achievements, we are now investigating the roles of other cancer-testis antigens in regulating genomic stability and also trying to clarify the functional links between the nuclear microenvironment and DNA repair or between cell cycle regulation and DNA repair. Recently, we have found that another cancer-testis antigen SYCE3 does not affect DNA repair but promotes cancer cell survival by regulating cell division throughout mitosis, indicating that cancer-testis antigens can induce genomic instability through various mechanisms.

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# Department of Osteoimmunology

## Project Associate Professor

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## Project Assistant Professor

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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, with the support of Noevir Co., Ltd., Chugai Pharmaceutical Co., Ltd. and AYUMI Pharmaceutical Corporation. 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).

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.

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<sup>+</sup> 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<sup>+</sup> 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 (Tsukasaka 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  $\gamma$ -chain ( $\gamma$ 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  $\gamma$ c and JAK3 (Inoue et al, *Nature Immunol*, 2018). This study presented a novel regulatory mechanism

governing  $\gamma$ 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<sup>+</sup> 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 about 10 years ago, the significance of the osteoblastic niche has 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 Continence Medicine

## Project Professor

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## Project Assistant Professor

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**Homepage:** <http://cont-med.umin.jp/>

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## Introduction and Organization

Our department has been established as an endowment department supported by Astellas Pharma Inc. in close collaboration with the Department of Urology on July 1st 2010 to facilitate researches specially focusing on continence medicine. Since July, 2013, this department has been received kind donations from six pharmaceutical companies (Astellas Pharma Inc., Asahi-kasei Pharma Corp., Ono Pharmaceutical Co., Ltd, Kissei Pharmaceutical Co., Ltd, Kyorin Pharmaceutical Co., Ltd, and Taiho Pharmaceutical Co., Ltd).

The aim of our department is to contribute to the advancement of continence medicine through basic and clinical researches on regulation mechanisms of lower urinary tract (LUT) function and pathophysiology of LUT dysfunction, as well as function/dysfunction of lower bowel and pelvic floor.

We believe that a multi-disciplinary professional team consisted of physicians, surgeons, nurses, physiotherapists, bio-engineers, social workers and scientists is necessary to achieve greater advancement of continence medicine and care. We hope many researchers with different specialties are interested in our research themes and collaborate with us for the purpose of supporting patients with continence problems by providing them better treatment and management strategies.

## Clinical activities

Professor Igawa offers clinical services specialized for patients with intractable lower urinary tract dysfunction as well as for children with urogenital disorders in conjunction with the Department of Urology.

## Teaching activities

We take part in providing systematic urological lectures for second year medical students, and bedside teaching for third and fourth year medical students.

## Research activities

We are currently investigating regulation mechanisms of lower urinary tract (LUT) function, and pathophysiological mechanisms of various LUT dysfunction, including overactive bladder (OAB), bladder outlet obstruction (BOO), interstitial cystitis/bladder pain syndrome(IC/BPS), and underactive bladder dysfunction, especially focusing on:

1. To elucidate bladder sensory transduction mechanisms
2. To disclose pathophysiology of development of detrusor overactivity/OAB
3. To find useful biomarkers for IC/BPS
4. To evaluate the effects of metabolic syndrome on LUT function

5. To develop novel pharmacological treatment for refractory LUT dysfunction
6. To establish continence-care system consisted of multi-disciplinary professionals to contribute to the advancement of continence medicine

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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, multidetector 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

## **Project Associate Professor**

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## **Project Academic Support Staff**

Satomi Kudo

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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

### English Article

1. Noguchi-Watanabe M, Maruyama-Sakurai K, Yamamoto-Mitani N, Matsumoto Y, Yoshie S, Iijima K, Yamanaka T, Akishita M. Community-based program promotes inter-professional collaboration among home healthcare professionals: A non-randomized controlled study. *Geriatr Gerontol Int.* 2019;19(7):660-666.
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### Conference Presentations

1. Yamanaka T (Lecture): Current Status and Prospect of Home Care Medicine in Japan: Homeward Medical Services. Parallel Session1 Integrated Healthcare and Community Care. The 10<sup>th</sup> Korea Healthcare Congress. Seoul, Korea, 2019.4.4.
2. Yamanaka T (Lecture): The Role of Home Care Medicine in Aging Society. 30<sup>th</sup> Anniversary symposium of Department of Family Medicine, Asan Medical Center. Seoul, Korea, 2019.6.14.
3. Yamanaka T (Lecture): Home Care Medicine in Japan. China international health care industry EXPO (Jinan) and medical care high-level summit. Jinan, Shandong, China, 2019.6.16.
4. Yamanaka T (Lecture): Comprehensive Geriatric Assessment and Nutritional Management in Home Care Medicine. International Training Workshop of Home Care. Tai'an, Shandong, China, 2019. 6.17.
5. Yamanaka T (Lecture): Diagnostic devices used in home medical care and medical therapeutic management at home. International Training Workshop of Home Care. Tai'an, Shandong, China, 2019.6.17.
6. Yamanaka T (Lecture): Chronic heart failure management at home. International Training

Workshop of Home Care. Tai'an, Shandong, China, 2019.6.18.

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# Department of Therapeutic Strategy for Heart Failure

## Research Associate Professor

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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 nine 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 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. When some symptom or findings which suggest rejection are detected, patients will undergo 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 2<sup>nd</sup> grade of medical course. We also take charge in clinical practice on diagnosis of cardiovascular disease in the autumn term at the 2<sup>nd</sup> 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 1<sup>st</sup> and 2<sup>nd</sup> grade. Joint lectures with the Cardiology Department are scheduled 3<sup>rd</sup> through 4<sup>th</sup> 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 3<sup>rd</sup> 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 10<sup>th</sup> 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 the every field of medical and surgical heart failure treatment, 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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# Department of Biostatistics and Bioinformatics

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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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# Department of Advanced Cardiology

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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

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### History and Organization Overview

Although the average person may not know about the revolutionary changes that are currently taking place, we have entered the dawn of a new age in which drugs are utilized more efficiently and delivered more reliably in regional health care, leading to improved patient outcomes. Regional formularies are being established, combatting polypharmacy has become the biggest issue confronting clinicians (as revealed by the results of a questionnaire survey), methodologies for implementing refillable prescriptions in Japan are being put in place, and the Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices has come fully into effect. A major rearrangement of the medical device landscape is underway, and collaboration between physicians and pharmacists is becoming more important in regional health care.

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. To date, it has not been possible to formulate measures for solving these problems because of a lack of evidence.

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. 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.

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# Department of Molecular Structure and Dynamics

## Project Professor

Nobutaka Hirokawa, M. D.

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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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Kunii Ya, Yoshikawa T., Tanaka Y., and N. **Hirokawa**. Betaine ameliorates schizophrenic traits by functionally compensating KIF3-based CRMP2 transport. *Cell Reports* in press

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# Department of Molecular Neurology

## Professor

Shoji Tsuji, M.D., Ph.D.

## Associate Professor

Jun Mitsui, M.D., Ph.D.

## Assistant professor

Takashi Matsukawa, M.D., Ph.D.

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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 Q<sub>10</sub> to patients with MSA could benefit patients because *COQ2* encodes the enzyme essential for the biosynthesis of coenzyme Q<sub>10</sub>. Recent studies have reported decreased coenzyme Q<sub>10</sub> 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 Q<sub>10</sub>) 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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# Department of Molecular Sciences on Diabetes

## Project Associate Professor

Hironori Waki, M.D., Ph.D.

## Project Research Associate

Masatoshi Kobayashi, M.D., Ph.D., Takayoshi Sasako, M.D., Ph.D.

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## Introduction and Organization

The prevalence of diabetes is rising to epidemic proportions worldwide. There is urgent need for development of the treatment for diabetes and related diseases. Advances in molecular biology had successfully led to elucidation of various mechanisms at a cellular level and at a tissue level in the physiological condition and in the disease states. In order to understand the precise mechanism underlying the development of diabetes, it is critical to reveal systemic connections between the cells and the tissues in the body.

The specific aims of our department are (1) to deepen and expand the investigations on metabolic tissues involved in glucose and lipid homeostasis, such as pancreatic endocrine cells, skeletal muscle, liver and adipose tissue and (2) to reveal the essential causes of diabetes from the perspective of the systemic network among the metabolic tissues.

## Teaching activities

As for the under-graduate education, our department takes a part in systemic lectures. We train graduate and post-graduate students in Nutrition and Metabolism, Internal Medicine, Graduate School of Medicine, The University of Tokyo.

## Research activities

Adipocyte and Energy Metabolism

Brown fat dissipates energy in the form of heat.

Increasing the mass or activity of brown fat is an attracting strategy for the treatment of obesity. We analyzed open chromatin genomic regions in brown fat and identified NFIA as a new transcription factor that controls brown-fat-specific gene program. NFIA binds to enhancers near brown-fat-specific genes and facilitates the binding of PPAR $\gamma$ —the adipocyte master regulator—to these enhancers. We further demonstrated its role by conducting experiments using culture cells, gene knock out animals, and epigenetic analysis using next generation sequencer. We also elucidated multiple activities and the roles of NFIA in the body by analyzing the effect of artificial mutations of NFIA and genetically engineered mice.

We also found that RNA N6-adenosine methyltransferase complex consisting of Wilms' tumor 1-associating protein (WTAP), methyltransferase like 3 (METTL3), and METTL14 positively controls adipogenesis by promoting cell cycle transition in the mitotic clonal expansion phase during adipogenesis. WTAP heterozygous knockout mice exhibited smaller adipocytes and were resistant to diet-induced obesity.

CDK5 Regulatory Subunit-Associated Protein 1-like 1 (CDKAL1) was identified as a susceptibility gene for type 2 diabetes and body mass index in genome-wide association studies. We found that CDKAL1 is expressed in adipose tissue and its expression is increased during differentiation. Stable overexpression of CDKAL1, however, inhibited adipocyte differentiation of 3T3-L1 cells, whereas knockdown of CDKAL1 promoted differentiation. CDKAL1 increased protein levels of  $\beta$ -catenin and its

active unphosphorylated form in the nucleus, thereby promoting Wnt target gene expression, suggesting that CDKAL1 activated the Wnt/ $\beta$ -catenin pathway—a well-characterized inhibitory regulator of adipocyte differentiation. Our results identify CDKAL1 as a novel negative regulator of adipocyte differentiation and provide insights into the link between CDKAL1 and metabolic diseases such as type 2 diabetes and obesity. We generated mice overexpressing CDKAL1 in adipose tissue and showed that these mice are protected from obesity under a high-fat diet.

#### Liver and Energy Homeostasis

Dynamic metabolic changes occur in the liver during the transition between fasting and feeding, which contributes to the maintenance of systemic homeostasis of glucose and lipid metabolism.

We have found that transient endoplasmic reticulum (ER) stress responses in the liver following feeding terminated by stromal cell-derived factor 2 like 1 (Sdf211) are essential for normal glucose and lipid homeostasis. In obese and diabetic mice, however, Sdf211 is downregulated, whereas restoration of Sdf211 expression ameliorates glucose intolerance and fatty liver with decreased ER stress. In diabetic patients, insufficient induction of Sdf211 correlates with progression of insulin resistance and steatohepatitis. Therefore, failure to build an ER stress response in the liver may be a causal factor in obesity-related diabetes and nonalcoholic steatohepatitis, for which Sdf211 could serve as a therapeutic target and sensitive biomarker.

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# Department of Immunotherapeutics

## Project Professor

Kazuhiro Kakimi, M.D., Ph.D.

## Project Assistant Professor

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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.

## Clinical activities

We provide outpatient services for cancer patients. All interventions performed in the department are defined by the protocols based on the Act on Securement of Safety of Regenerative Medicine

(Approved on Nov 20, 2013). The following clinical trials were conducted in our department:

### $\gamma\delta$ T cell therapy for advanced cancer

1. UMIN registration number : UMIN000006128 active, recruiting. Adoptive immunotherapy using zoledronate-expanded autologous  $\gamma\delta$  T cells for patients with non-small cell lung cancer refractory to standard treatment.

### Immunomodulator

(anti-CCR4 mAb+anti-PD-1mAb)

1. UMIN-CTR Clinical Trial ID : UMIN000021480. ClinicalTrials.gov ID : NCT02946671. Study of Pre-operative Combination Therapy with Mogamulizumab and Nivolumab Against Solid Cancer Patients

## 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

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 $\gamma$ , microsatellite instability, somatic copy-number alterations, HLA class I diversity, T cell repertoire clonality change, WNT- $\beta$ -catenin signaling, TGF $\beta$  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.

## List of Publications

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- 3) Sugimoto K, Kakimi K, Takeuchi H, Fujieda N,

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## **Presentation at International conference**

- 1) 2019/6/6-7. The 26th International Symposium on Molecular Cell Biology of Macrophages MNCB2019. Tokyo. Koji Nagaoka, Akihiro Hosoi, Changbo Sun, Kiyomi Taniguchi, Masataka Shirai, Kazuhiro Kakimi. Early activation of myeloid cells is required for the CD8<sup>+</sup> T-cell dependent anti-tumor immunity
- 2) 2019/9/9. 2019 World Conference Lung Cancer (IASLC). Barcelona, Spain. T. Karasaki, Y. Kobayashi, A. Shinozaki-Ushiku, C. Konoeda, K. Kitano, K. Nagayama, M. Sato, A. Hosoi, K. Kakimi, J. Nakajima. TUMOR SPREAD THROUGH AIR SPACES IS ASSOCIATED WITH THE NON-INFLAMED IMMUNE MICROENVIRONMENT IN LUNG SQUAMOUS CELL CARCINOMA

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# Department of Immunotherapy Management

## **Project Associate Professor**

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## **Project Associate**

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## **Introduction and Organization**

Recently, biologic agents targeting cytokines or cell surface molecules and small molecules targeting intracellular pathways relevant to cytokine production or cytokine signaling, play an important role in the treatment of autoimmune diseases. Both of them are named as molecularly targeted drugs. In Japan, these molecularly targeted drugs are available for the treatment of rheumatoid arthritis, psoriasis, Behcet disease and inflammatory bowel diseases. These diseases are treated in the Department of Allergy & Rheumatology, Dermatology, Orthopedics Gastroenterology, Surgical oncology & vascular surgery, and Ophthalmology. The Department of Immunotherapy Management was established in April 2013, and renewed through donations from new seven pharmaceutical companies (Mitsubishi-Tanabe, Chugai, Ayumi, Taishotoyama, Nipponkayaku, UCB Japan, Abbvie) in June 2016. The Department of Allergy & Rheumatology, Dermatology and Orthopedics work in collaboration.

Biologics agents include infliximab, infliximab BS, adalimumab, golimumab, certolizumab pegol, etanercept, tocilizumab, abatacept, ustekinumab, secukinumab, ixelizumab, brodalumab, guselkumab, rituximab, mepolizumab and belimumab. The Jak kinase inhibitors include tofacitinib and baricitinib. These molecularly targeted drugs have been developed in succession. However, it is difficult to predict the efficacy and toxicity of these agents by the

background characteristics of patients with rheumatoid arthritis. The aims of this department are to propose an optimal treatment strategy for each patient and to establish a platform to investigate novel biologics through analyses of immunological changes by molecularly targeted therapy and the relationship between biologics response and biomarkers or genetic information.

## **Clinical activities**

We established a new booth for outpatients with rheumatoid arthritis who are receiving molecularly targeted drugs which is available every morning from Monday to Friday. We focus on total rheumatoid arthritis care with molecularly targeted drugs. Moreover, we examine outpatients with psoriasis, spondyloarthritis and Behcet's disease before molecularly targeted therapy and judge whether these treatments can be used safely. In every Friday afternoons, we evaluate for outpatient with psoriatic arthritis including accurate diagnosis and monitoring disease activity by clinical and imaging examinations.

## **Teaching activities**

As for education, we take part in providing information of molecularly targeted drugs for patients who are the candidates to receive biologics, including necessity, benefits, safety, complications, procedures and costs. Every time when a new molecularly targeted drug becomes available for prescription, we



provide information of the agent for medical staffs. Moreover, we are giving lectures about molecularly targeted therapy for medical students at bed-side learning programs or at systematic lecture courses.

## Research activities

As for research, we are investigating novel molecularly targeted drugs through analyses of immunological changes by molecularly targeted therapy and the relationship between biologics response and biomarkers or genetic information.

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# Department of Ubiquitous Preventive Medicine

## Associate Professor

Yuichi Ikeda, M.D., Ph.D.

## Assistant Professor

Kazutaka Ueda, M.D., Ph.D.

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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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2. Ueda K, Toko H, Komuro I. Endothelial cell-derived angiocrines elicit physiological cardiomyocyte hypertrophy. **Circulation.** 139:2585-2587,2019
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# Department of Life Support Technology (Molten)

## **Project Professor**

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## **Project Lecturer**

Hiroshi Noguchi, Ph.D.

## **Project Assistant Professor**

Toshiaki Takahashi, Ph.D.

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## **Introduction and Organization**

Department of Life Support Technology (Molten) was founded Oct. 1, 2010 as a laboratory in Graduate School of Medicine of the University of Tokyo.

The aim of the department is to establish life support technology, which include not only pathophysiology investigation of diseases and symptoms caused by daily life activities but also development of direct intervention method based on nursing approach and methodology establishment for supporting daily life widely.

First, Prof. Hiromi Sanada, who drives translational research in nursing research area, and Molten Corp., which is one of Japanese welfare device development companies, planned to establish this department. After planned, Prof. Takeyoshi Dohi, leading person in welfare and medical device engineering, recommended Taketoshi Mori, Ph.D. as a leader of the department. He arrived at his post and the department was established.

From Oct 1, 2015, the second term of the department started. On Feb 20, 2016, the celebration party for department continuation and promotion of Prof. Mori was held at Gakushi-Kaikan, which is the same place as the celebration party for department establishment.

Many people including president of Molten Corp. Kiyoshi Tamiaki, Prof. Noriko Yamamoto and Prof. Takeyoshi Dohi attended the party. Both nursing researchers and engineering researches congratulate the department continuation and promotion of Prof. Mori.

Our department contributed to establishment of the society for nursing science and engineering from 2012. The first annual meeting of nursing science and engineering was hold at 5<sup>th</sup> Oct 2013. Our department played a great important role for management of the meeting as a host.

From Apr 1, 2017, global nursing research center was established in Graduate School of Medicine of the University of Tokyo. In the center, Project Prof. Mori held the addition concurrent post of Robotic Nursing in Division of Care innovation.

Current members include a project professor, a project lecturer and a project assistant professor. We accept students from Division of Health Science and Nursing. Accepted two master course students were graduated at the end of 2013. The supportive department is the Department of Gerontological Nursing / Wound Care Management. We also accept foreign students. In 2013, we accepted a Ph.D. student from Mexico. In 2017,

we accepted a research student from Korea. The student was a 2<sup>nd</sup> year student of Division of Health Science and Nursing.

## Teaching activities

As for lectures, our department assisted the lectures of the supportive department, the Department of Gerontological Nursing/Wound Care Management. In a part of Wound Care Management I for graduate course, Taketoshi Mori taught electric engineering, which is closely related to development of medical and nursing devices. Hiroshi Noguchi taught measurement engineering. We invited engineering professors outside the university for Gerontological Nursing II for graduate course. In a part of Gerontological Nursing I for graduate course, the members in the department lectured the features and reading method of journal papers of engineering research based on typical publications.

As for the other education activity, our department supported management of the seventh seminar for nursing science and engineering, which was organized by global nursing research center. The staffs in our department had engineering-related lectures.

From establishment of global nursing research center, the laboratory have accepted training or visitation in our laboratory 15 times (7 from foreigners, and 8 from domestic visitors)

## Research activities

Our research themes are to investigate causes of diseases and/or wounds due to daily life activity, and to develop instrument for effective monitoring and preventing diseases and/or wounds. We study science and technology of natural human monitoring, nursing engineering, and human behavior sensing thoroughly.

We are seeking a new interdisciplinary research domain between engineering and nursing, and willing to realize comfortable daily life through these researches.

We are developing the methodology to support healthy and comfortable daily life by 1) monitoring daily life

naturally, 2) understanding the typical behaviors, and 3) predicting diseases, injuries, and accidents using various sensing technology.

Main themes of our department are the following:

- a) Development of monitoring systems for patient on a bed and vital sign measurement system using mattress
- b) Construction of behavior measurement in daily living environment using simple sensors and algorithm for typical behavior pattern extraction and transition estimation of human behavior pattern
- c) Three-dimensional leg movement measurement and spatiotemporal 3D leg state measurement for prevention of foot ulcer
- d) Clinical research and image processing technology development for current status and management of incontinence
- e) Human position measurement and behavior estimation using laser range scanners
- f) Design and construction of human behavior database

As for the clinical field, we started the research at the University hospital using communication robots from 2017. From 2018, we extended the robot research field to another facility with Department of Gerontological Nursing/Wound Care Management.

The master course student, who was belonging to our department, developed a new non-invasive device to estimate skin condition online and onsite using electric-impedance tomography for assessment of pressure ulcer healing condition. He wrote master course thesis “Developing a pressure ulcer monitoring tool using electrical impedance tomography and spectroscopy: Phantom study and preliminary human trial” and graduated.

We achieved the following award in this year.

1. Presentation award of Japanese Society of Wound, Ostomy, and Continence Management (domestic conference). Takeo Minematsu, Michitaka Ogata, Nao Tamai, Koichi Yabunaka, Tomonori Maeda, Gojiro Nakagami, Hiroshi Noguchi, Hiromi Sanada “Deep tissue injury actual situation among wheel chair basket

athletes: skin properties related to deep tissue injury”. Proceedings of the 28<sup>th</sup> annual conference of Japanese Society of Wound, Ostomy, and Continence Management. Vol.23, No. 2, pp. 242, 2019.

2. Presentation award of Japanese Society of Pressure Ulcer (domestic conference). Tomonori Maeda, Nao Tamai, Takeo Minematsu, Hiroshi Noguchi, Gojiro Nakagami, Koichi Yabunaka, Hiromi Sanada. “Relationship between hip pressure during playing and pressure ulcer occurrence among wheel chair basketball athlete”, Proceedings of Japanese Society of Pressure Ulcer. Vol.21, No. 3, pp. 309, 2019.

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# Department of Clinical Trial Data Management

## **Project Assistant Professor**

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Takuhiro Yamaguchi, Ph.D.

## **Registered Researcher**

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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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# 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 March 1st, 2017, which is an endowment department supported by Chugai Pharmaceutical Co., Ltd., Fujifilm Corporation, Ajinomoto Co., Inc., ASAHI KASEI PHARMA CORPORATION, ALCARE Co., Ltd., Inter Reha Co.,Ltd., Anima Corporation, TEIJIN PHARMA LIMITED, Suntory Holdings Limited, Hisamitsu Pharmaceutical Co., Inc., 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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# **Social Cooperation Program**

# Department of Advanced Nursing Technology

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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. This center was 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 inter-

disciplinary 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 2019 was titled "Incidence, characteristics and timing of peripheral intravenous catheter failure in patients receiving chemotherapy with hematological malignancy; a prospective descriptive study."

We were in charge of lectures on nursing translational research at the seminar hosted by GNRC for post-doctoral fellows and other researchers. (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 2019

- Understanding the mechanisms that lead to peripheral intravenous catheter failures: PIV-CF.
- Development 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**

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## **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 Mikihiko Karube (FUJIFILM Corp.). The Project Associate Professor concurrently served as a member at a visualized nursing field of Division of Care Innovation, the Medical Graduate School of Global Nursing Research Center and now strives to establish and disseminate imaging nursing skills in nursing research.

## **Education**

In 2019, we provided the following lectures for undergraduate and postgraduate students.

- a) Human Anatomy (A1 in 3rd yr.)
- b) Bioengineering Nursing (S2 in 4th yr.)
- c) Laboratory Practice for Life Science II (S2 in 3rd yr.)
- d) Practicum in Human Health Support (W in 2nd yr.)

- e) Gerontological Nursing (A2 in 4th yr.)
- f) Special Lecture in Gerontological Nursing I (S1)
- g) Special Lecture in Wound Care Nursing I (S2)
- h) Special Lecture in Wound Care Nursing II (A)

We instructed and cooperated with graduate students of the Department of Gerontological Nursing / Wound Care Management regarding 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 as well as on skin tears in the Adachi Community Health Center and Keiyu Hospitals.

At the seminar on nursing science and engineering, sponsored by the Global Nursing Research Center, we lectured on imaging nursing skills to many nursing researchers and clinical nurses. In addition, we gave hands-on training in ultrasound technology and qualitative sketching techniques useful for nursing to interested participants.

## 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 in our Japan Agency for Medical Research and Development-funded study titled, "Constructing a multidisciplinary system implementing advanced nursing techniques to support eating and defecating in patients receiving home and facility care." We have developed the support systems of "eating," "elimination," and "skin/wound care" using ultrasound devices:

- 1) Development and assessment of a home/long-term care facility multidisciplinary system to support eating and swallowing.
- 2) Development and assessment of a home/long-term care facility multidisciplinary information and communication technology system to support bowel elimination.
- 3) Development of an educational program for deep tissue injury using artificial intelligence.

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

- Best Moderated Poster Award from the 8th Asia Pacific Enterostomal Therapy Nurse Association (2019, Nov). Ayano Nakai, Toshihiro Tsukatani, Nao Tamai, Tamae Urai, Yukie Mori, Kuang Weijie, Takeo Minematsu, Chika Takada, Hiromi Sanada. Relationship between type IV collagen positivity via skin blotting and conventional risk factors of skin tears.
- Best Presentation Award from the 21st Annual Congress of Japanese Society of Pressure Ulcers (2019, Aug). Tomonori Maeda, Nao Tamai, Takeo Minematsu, Hiroshi Noguchi, Gojiro Nakagami, Koichi Yabunaka, Hiromi Sanada. Relationship between pressure ulcers and dynamic buttock pressure distributions during performance in wheelchair basketball athletes.
- Best Presentation Award from the 28th Japanese Society of Wound, Ostomy & Continence Management (2019, May). Takeo Minematsu, Michitaka Ogata, Nao Tamai, Koichi Yabunaka, Tomonori Maeda, Gojiro Nakagami, Hiroshi Noguchi, Hiromi Sanada. Skin properties related to deep tissue damage in wheelchair basketball athletes.

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# Department of Healthcare Quality Assessment

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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.

## Research activities

Department of Healthcare Quality Assessment (HQA) has been actively collaborating with healthcare professionals and various clinical committees as they play key roles in the quality improvement initiatives in the field. In such positive environment driven by the patient-centered philosophy, the patients receive more satisfying care, physicians are rewarded for their excellence, and healthcare costs are sustained. To accomplish 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.

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# Voice Analysis of Pathophysiology

## Project Associate Professor

Shinichi TOKUNO, M.D.,Ph.D.

## Project Assistant Professor

Mitsuteru NAKAMURA, Ph.D.

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## Introduction and Organization

Department of Voice Analysis of Pathophysiology was established as a Social Cooperation Program on September 2014, funded by Mazda Co., Ltd. and MKI (Mitsui Knowledge Industry) Co., Ltd. Professor Yahagi, Emergency and Critical Care Medicine, assisted us at that time. From September 2017, We funded by Mazda Co., Ltd. and PST Inc. Professor Yamada, Anesthesiology, assisted us at that time.

Purpose of our department is “to establish Verbal Analysis of Pathophysiology as academic In order to build a safe and secure society in which those who need emergency medical care can reach timely and appropriate emergency medical care. That is followed to build a system to support an approach to emergency medical care not only after onset of the disease but also before onset of the disease in daily life”.

In general, the physician discerns a qualitative change in the patient's voice and inferred his/her medical condition. Verbal Analysis of Pathophysiology Technology is to visualize the condition of the patients from his /her voice, to assist in the diagnosis, treatment and prevention. Verbal Analysis of Pathophysiology academically organized this technology, and visualizes the disease by using the biometric information of the voice which has not been so far utilized

Faculties were Shinichi TOKUNO, M.D.,Ph.D., Project Associate Professor, Mitsuteru NAKAMURA, Ph.D., Project Assistant Professor and one project researchers. Additionally, two guest researchers will attend our department.

## Teaching activities

Shunji MITSUYOSHI, Project Lecturer was performing a lecture about overview of the verbal analysis of pathophysiology technology (PST: Psychoanalysis System Technology) and the voice emotion recognition technology (ST: Sensibility Technology) underlying PST in the department of engineering.

## Research activities

It includes voluntary component such as language and involuntary component which is mainly derived from the autonomic nervous in voice. Voice emotion recognition technology which recognizes an emotion of the speaker by assessing patterning the involuntary component has already been established. Our research forces on the assessment of the medical validity of the verbal analysis of pathophysiology technology (PST: Psychoanalysis System Technology) which measure the health of mind (depressive or manic) from the voice, and the research for the society implementation of this technology. Additionally, we will further develop this technology, and try to applicate it to the other diseases.

- Research for medical verification and social implementation of depression evaluation by voice

- 1) Voice comparison of healthy subjects and patients

Currently, by analyzing the voice for long term about two weeks, it was possible to substantially identify the voice of patients and healthy subjects. In the future, to increase the accuracy, we will increase the number of cases.

- 2) A study on the monitoring of health status by voice using a smartphone

As a social implementation research, we are conducting prospective research on long-term use by volunteers.

- 3) Use in industrial hygiene field of stress check by voice

As research for social implementation, we are conducting a study to use our technology in the context of industrial hygiene.

- 4) Verification in other languages

In order to confirm the usefulness of languages other than Japanese, we are conducting a joint research of the speech database of the foreign languages and other countries.

- 5) The detailed study by multicenter study

Because of the robustness evaluation of technology, we are conducting joint research in the multi-center.

- Application of the verbal analysis of pathophysiology technology to other than the stress-depression

We perform the joint research with Mazda Co., Ltd., which our investment company.

- 1) sleep apnea syndrome

By the analysis of voice in the awakening and snoring in falling asleep of the patients who have sleep apnea syndrome, we have done research on the measurement of the quality of sleep.

- 2) Application to other diseases

We are currently conducting research on psychiatric disorders (major depression, bipolar disorder), neurological disorders (Parkinson's disease), dementia (including Alzheimer's disease), oral surgery diseases (tongue adhesions) and so on.

- A study for the effects of driving a car on the health of maind

We perform the joint research with Mazda Co., Ltd., which our investment company.

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# Department of Ubiquitous Health Informatics

## Associate Professor

Waki Kayo, M.D., M.P.H., Ph.D.

## Researcher

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## Introduction and Organization

Our mission is to promote research and development of a novel integration system in which pieces of patients' healthcare information are virtually combined and stored separately in diverse medical/ healthcare facilities. Recently developed mobile information communication technologies (ICT)—in conjunction with cloud computing—provide a sturdy environment in which to build a “virtual ubiquitous health information space.” We particularly focus on better clinical outcomes in various medical/healthcare fields, as well as the efficacy, safety, and security achieved by these innovative systems. This department has finished in August 2019. The following researches are taken over by Department of Healthcare Information Management, The University of Tokyo Hospital.

## Research activities

- *DialBetics: A novel smartphone-based self-management support system for type 2 diabetes patients*

Patients with diabetes are expected to have access to the integral components of diabetes care. Self-management is the core of diabetes treatment because it ties the components of diabetes therapy together, enabling patients to assess and control the interplay of nutrition, physical activity, emotional/physical stress, and medications that are critical with diabetes. There had long been a need for an effective self-management tool that could automate and standardize much of the counseling

process, facilitating self-monitoring of blood glucose, blood pressure, body weight and lifestyle, and particularly diet and exercise. Accordingly, we developed just such a real-time, partially automated interactive system to interpret patients' data—biological information, exercise, and diet content calculated from a message sent by patients—and respond with appropriate actionable findings, helping the patients achieve diabetes self-management. In addition, the safety and clinical effectiveness of the system had to be examined. A one-month, non-blinded, non-randomized uncontrolled study was conducted; it demonstrated that DialBetics was a feasible and effective tool for type 2 diabetes patients who also received insulin therapy. We conducted a 3-month clinical trial for type 2 diabetes patients using DialBetics in Pavia, Italy. The effectiveness of this system was also confirmed in Italy. In our latest study, we conducted a questionnaire survey that adopts AI technology as a function of DialBetics for diabetic patients. Based on our previous findings, we started a new study—a randomized clinical study—among patients with diabetic kidney disease (DKD). DKD is a known risk factor for end-stage renal disease, cardiovascular disease, and all-cause death. One method to evaluate DKD is to identify abnormal urinary albumin excretion. Effective intervention for early-stage DKD is important to slow the progression of kidney disease and improve prognoses. The purpose of the study is to evaluate the efficacy of the addition of a self-management system, DialBeticsPlus, to a ~~standard~~ conventional therapy in DKD patients with microalbuminuria. This study is a prospective, randomized,

open-label, multicenter clinical trial. The target population consists of 160 patients (age  $\geq 20$  years) diagnosed with DKD accompanied with micro-albuminuria. We will randomize the patients between the two groups—the intervention group that uses DialBeticsPlus in addition to a conventional therapy and the control group that only receives a conventional therapy. DialBeticsPlus is a modified version of DialBetics. The study period is 12 months, with a follow-up survey at 18 months. The primary outcome for this study is change in albuminuria levels measured in a first-morning void at 12 months. Secondary outcomes include changes in physical parameters, parameters of glycemic control, lipid metabolism and renal function, lifestyle habits, self-management scores, medication therapy, adherence to oral hypoglycemic agents, and quality of life. Additional evaluations will be made of all-cause death, composite cardiovascular outcomes, composite renal endpoint, efficacy of “hospital-led” and “dispensing-pharmacy-led” methods of deploying DialBeticsPlus, safety, and usage pattern of DialBeticsPlus. The study was approved in April 2018. We began recruiting patients in July 2018 and finished recruiting in August 2019. The final 18-months follow-up will be done in March 2021. The first results are expected to be published in 2021. We predict that albuminuria levels will decrease significantly in the intervention group. We also expect other parameters to improve after the intervention due to improved lifestyle habits and behaviors.

- *Glucote: Self-management and recording application for the type 2 diabetes and diabetes spare group*

We started a clinical study using a smartphone application with ResearchKit by Apple Inc. that is called "Glucote" for type 2 diabetes patients and diabetes spare group. This application continuously collects home vital data such as blood glucose level, blood pressure, weight, active mass, and also lifestyle data—dietary intake, exercise, and sleep. A total of 522 patients signed up for the study for the duration of one year. It was indicated that patients who continue to measure themselves—self-management—resulting in weight decrease. The results are published in the form of a refereed journal article.

- *Multi-institutional joint prospective study on arrhythmia detection efficiency by wearable heart rate monitor*

Cardiogenic cerebral infarction has a poor prognosis in that it leaves big sequelae, and its early detection is important. In order to investigate whether it is possible to capture pulse irregularities simply and conveniently, we planned research to monitor long-term heart rate using a wearable heart rate monitor that is on the market. We conducted clinical research for 100 workers who are at risk of developing cerebral infarction if they have atrial fibrillation, such as high blood pressure, diabetes, cerebral infarction, heart failure, etc. New atrial fibrillation was confirmed in two participants. It was suggested that atrial fibrillation can be detected by long-term electrocardiogram monitoring. The results are published in the form of a refereed journal article.

- *Inspection of the correlation of blood sugar level and expiration acetone measurements*

To diagnose ketoacidosis under diabetes mellitus require measurement of blood test and urinalysis. We studied the correlation of expiration acetone levels using portable expiration acetone measuring system and blood acetone levels. We conducted a clinical trial with 120 diabetic patients, and also investigated the variation of error within the same participants. A patent has been applied for.

- *Survey of medication, health care and intent to use personal health record in ethical pharmacy users.*

This survey was to clarify whether medication management requires PHR and what kind of items the users are required for the management of PHR. We surveyed 3,717 people and got responses from 2,307 people. Results were presented at the 37th joint conference on medical informatics. The results are published in the form of a refereed journal article.

- *DialBeticsLite for health guidance object persons*

Health guidance is a support program for people with metabolic syndrome to improve their lifestyle. We conducted a clinical trial to study the effect of DialBeticsLite and differences from type 2 diabetes patients using DialBetics for health guidance object persons in four companies. Notably, we (University of Tokyo hospital) made DialBeticsLite fit for practical use in a company. DialBeticsLite was used in three companies already.



- *DialBeticsStep for people with high risk of lifestyle-related disease*

Behavioral interventions based on behavioral theory were reported to increase the amount of exercise in patients with type 2 diabetes significantly. We incorporated behavioral theory in DialBetics to motivate users to increase the number of steps. A pilot study was conducted among participants with a high risk of lifestyle-related diseases. Preliminary results show that the application is effective in increasing the amount and encouragement of exercise.

#### ***Future directions***

To fulfill our mission, we plan to generalize the findings made in several clinical studies and promote ongoing and growing telemedicine service with the use of ICT in the future.

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# Department of Skincare Science

## Project Associate Professor

Takeo Minematsu, Ph.D

## Project Lecturer

Misako Dai, Ph.D., R.N., P.H.N., CLT.

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## Introduction and Organization

The Department of Skincare Science was established in the Graduate School of Medicine with funding from Saraya Co., Ltd. on February 1<sup>st</sup>, 2017. We try to develop new nursing technologies to evaluate and improve the physiological conditions of vulnerable skin due to aging and diseases.

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

## Teaching activities

In FY2019, we provided the following lectures for undergraduates, master course students, or Ph.D. course students:

- a) Gerontological Nursing in Gerontological Nursing (A2 in 3rd yr/ S1 in 4th yr)
- b) Clinical Practice (S2 in 4th yr)
- c) Bioengineering and Nursing (S2 in 4 th yr)
- d) Gerontological Nursing I (S1)
- e) Wound Care Management I (S2)
- f) Wound Care Management II (S2)

We advised graduate course students belonging to the Department of Gerontological Nursing/Wound Care Management on matters concerning research planning and practice work.

The following were master's and bachelor's research themes in 2019:

Master: "Polymorphism analysis of candidate risk genes for pressure ulcers in older Japanese patients: A cross-sectional study at a long-term care hospital"

Bachelor: "Development of the estimation method to

measure weight and body fat percentage for basketball athletes.

## Research activities

### 1. Activity policy

The skin is a unique organ which we can directly see and touch. Because several sensory systems are distributed in the skin, skin disorders have unique physical and mental influences. Healthy skin is, therefore, a foundation of a healthy life. The Department of Skincare Science was founded to establish skincare for people with vulnerable skin due to aging and dermatopathy.

Our project associate professor was also in charge of the Department of Biological Nursing, Division of Care Innovation, Global Nursing Research Center, and worked to establish and spread methodologies to study the biological properties of nursing problems.

We delivered lectures about analytical thinking processes and physiological/molecular biology techniques for many nursing researchers and clinical nurses in the bioengineering nursing research seminar organized by Global Nursing Research Center on July 2019. We furthermore organized an advanced hands-on seminar of bioengineering nursing research methodologies on February 2020.

### 2. Research themes in 2019

Since February 2017, we have worked with Saraya Co., Ltd., to develop new nursing technologies using wound blotting for application in clinical setting. After launched in 2018, this new product has been applied in many facilities. In furtherance of this effort, we

have also contributed to the 2020 Tokyo Paralympic Games through pressure ulcer care for wheelchair athletes.

- Development of non-invasive skin assessment methods using skin blotting
  - Evaluation of skin barrier functions
  - Detection of tinea pedis
  - Detection of dehydration
  - Predictive validity of skin blotting for skin tear development
- Development and practical realization of wound assessment methods using wound blotting
  - Prediction of pressure ulcer healing
  - Detection of wound biofilm
  - Effects of medical wigs during chemotherapy
- Pressure ulcer care in wheelchair athletes
  - Survey of pressure ulcers
- Skin regenerative medicine
  - Survey of pressure ulcers
- Development of scaffold materials to regenerate ultrastructure of epidermis
- Development of predictive scoring tool for skin tear
- Development preventive care for recurrent cellulitis with lymphoedema
  - Identify the biomarkers for recurrent cellulitis with lymphoedema
  - Development of ultrasound assessment method for lymphoedema patients

Our research was recognized in the form of several awards, as follows:

- The 8th Asia Pacific Enterostomal Therapy Nurse Association, Best Moderated Poster Award. Minematsu T, Tsukatani T, Weijie K, Nakai A, Tomida S, Nakagami G, Sanada H. Intra-rater reliability of albumin measurement by skin blotting in healthy volunteers. The 8th Asia Pacific Enterostomal Therapy Nurse Association, Taipei (Taiwan), 2019/11/22.
- The 8th Asia Pacific Enterostomal Therapy Nurse Association, Best oral Award. Nakagami G, Sanada H, Mori Y, Minematsu T, Kitamura A. Biofilm-based wound care system for treating chronic wounds. The 8th Asia Pacific Enterostomal Therapy Nurse Association, Taipei (Taiwan), 2019/11/22.
- The 8th Asia Pacific Enterostomal Therapy Nurse Association, Best Moderated Poster Award. Nakai A, Tsukatani T, Tamai N, Mori Y, Weijie K, Minematsu T, Takada C, Sanada H. Relationship between type IV collagen positivity via skin blotting and conventional risk factors of skin tears. The 8th Asia Pacific Enterostomal Therapy Nurse Association, Taipei (Taiwan), 2019/11/22.
- 2019 Skin Integrity Summer School. Best Innovation Poster Award. ILF Japan (Sanada H, Sugama J, Dai M, Nakagami G). LIMPRINT reporting from ILF Japan.
- Good Design Award Office, Japan Institute of Design Promotion. Good Design Award. Elastic stocking for patients “Cool lala”. Batel Plus Corporation, Yoshida Tsukasa Co., LTD., Dai M, Murayama H.

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# Department of Prevention of Diabetes and Lifestyle-Related Diseases

## **Project Associate Professor**

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## **Project Assistant Professor**

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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 are analyzing 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 are analyzing 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

## Project Associate Professor

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## Project Assistant Professor

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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

In 2018, Department of Innovative Dementia

Prevention was involved in the education through research activities of two doctor course graduate students of the Graduate School of Medicine, one doctor course graduate student of the School of Pharmaceutical Sciences, one master course graduate students of the Graduate School of Medicine, as well as one 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 $\beta$  dynamics in the brain

Amyloid  $\beta$  peptide (A $\beta$ ), a causative protein for AD, is produced from A $\beta$  precursor protein (APP) through two-step proteolysis by  $\beta$ - and  $\gamma$ -secretases, and then secreted into the extracellular space. Once released outside the neurons, A $\beta$  is readily cleared by proteolytic degradation or transported outside the brains. However, A $\beta$  that escaped from the clearance starts to aggregate and deposit forming amyloid fibrils. Thus, the elucidation of the A $\beta$  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 $\beta$  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 $\beta$  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 $\beta$  and evaluate the following A $\beta$  deposition (Hori Y, *et al.*, *J. Biol. Chem.*, 2015), we have identified a >200 kDa high molecular weight A $\beta$  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 $\beta$  species that are involved in the A $\beta$  dynamics in the brain, including those specifically involved in deposition or toxicity of A $\beta$ .

- 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 ( $\epsilon 2$ ,  $\epsilon 3$ ,  $\epsilon 4$ ), 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 $\epsilon 4$  allele is ~8-10% in normal population, whereas it is elevated to >30-40% in AD. Thus, ApoE $\epsilon 4$  is a strong genetic risk factor of AD, although the mechanism whereby ApoE $\epsilon 4$  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 $\beta$  dynamics in the brain. This will lead us to the intervention into the effect of apoE isoforms on A $\beta$ , toward the goal of AD prevention. In

2017, we have found a significant decrease in A $\beta$  deposition in the brains of human apoE3 KI/APP transgenic mice. In 2018, we have also found that apoE3 reduced the deposition of A $\beta$  compared with murine apoE using *in vivo* seeding technique. We also found that the A $\beta$  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 $\beta$  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 $\beta$ .

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

Based on epidemiological and experimental studies, type 2 diabetes mellitus (T2DM), especially insulin resistance that comprises the core mechanism of T2DM, has been recognized as a significant risk factor for AD. However, the molecular mechanisms linking between T2DM and AD is not fully understood yet. To study the causal relations and molecular mechanisms underlying insulin resistance-induced exacerbation of amyloid pathology, we investigated the chronological changes in the development of insulin resistance and amyloid pathology in two independent insulin-resistant AD mouse models, i.e. long-term high-fat diet (HFD) feeding and genetic disruption of *Irs2*, in combination with dietary interventions.

In this year, we found that HFD-fed diabetic AD model mice displayed a reduced brain response to peripheral insulin stimulation and a decrease brain to plasma ratio of insulin during the hyperinsulinemic clamp. Diet-induced defective insulin action in the brain was accompanied by a decreased clearance of the extracellular A $\beta$  in vivo and an exacerbation of brain amyloid pathology (Wakabayashi T, *et al.*, Mol Neurodegener, 2019).

## Publications

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# Department of Health Services Research

## **Project Associate Professor**

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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 2019.

### 1) Hospital Volume and Mortality following Diagnostic Bronchoscopy in Lung Cancer Patients: Data from a National Inpatient Database in Japan

Recent advances in bronchoscopy utilizing endobronchial ultrasound (EBUS) as well as lung cancer therapy may have driven physicians to perform diagnostic bronchoscopy (DB) for high-risk patients. The aim of this study was to clarify the relationship between hospital volume (HV) and outcomes of DB.

We collected data on inpatients with lung cancer who underwent DB from July 2010 to March 31, 2014. The annual HV of DB was classified as “very low” ( $\leq 50$  cases/year), “low” (51–100 cases/year), “high” (101–300 cases/year), or “very high” ( $> 300$  cases/year). The primary outcome was all-cause 7-day mortality after DB. Multivariable logistic regression fitted with a generalized estimation equation was performed to evaluate the association between HV and all-cause 7-day mortality after DB, adjusted for patient background factors.

We identified a total of 77,755 eligible patients in 954 hospitals. All-cause 7-day mortality was 0.5%. Compared with the low-volume group, 7-day mortality was significantly lower in the high-volume group (odds ratio [OR] = 0.69, 95% confidence interval [CI]: 0.52–0.92,  $p = 0.010$ ), and a similar trend was shown in the very-high-volume group (OR = 0.67; 95% CI: 0.43–1.05,  $p = 0.080$ ). Radial EBUS with the guide sheath method and EBUS-guided transbronchial needle aspiration showed a significantly lower 7-day mortality.

All-cause 7-day mortality was inversely associated with HV. The risk of DB in patients with lung cancer should be recognized, and the exploitation of EBUS may help reduce mortality after DB.

### 2) Reduction in exacerbation of COPD in patients of advanced age using the Japanese Kampo medicine Dai-kenchu-to: a retrospective cohort study

Patients with symptomatic COPD are recommended to use inhaled bronchodilators containing long-acting muscarinic receptor antagonists (LAMAs). However, bronchodilators may cause gastrointestinal adverse effects due to anticholinergic reactions, especially in advanced-age patients with COPD. Dai-kenchu-to (TU-100, Da Jian Zhong Tang in Chinese) is the most frequently prescribed Japanese herbal Kampo

medicine and is often prescribed to control abdominal bloating and constipation. The purpose of this study was to evaluate the role of Dai-kenchu-to as a supportive therapy in advanced-age patients with COPD.

We used the Japanese Diagnosis Procedure Combination inpatient database and identified patients aged  $\geq 75$  years who were hospitalized for COPD exacerbation. We then compared the risk of re-hospitalization for COPD exacerbation or death between patients with and without Dai-kenchu-to using 1-to-4 propensity score matching. A Cox proportional hazards model was used to compare the two groups. We performed subgroup analyses for patients with and without LAMA therapy.

Patients treated with Dai-kenchu-to had a significantly lower risk of re-hospitalization or death after discharge; the HR was 0.82 (95% CI, 0.67–0.99) in 1-to-4 propensity score matching. Subgroup analysis of LAMA users showed a significant difference in re-hospitalization or death, while subgroup analysis of LAMA non-users showed no significant difference.

Our findings indicate that Dai-kenchu-to may have improved the tolerability of LAMA in advanced-age patients with COPD and, therefore, reduced the risk of re-hospitalization or death from COPD exacerbation. Dai-kenchu-to may be recommended as a useful supportive therapy for advanced-age patients with COPD.

### 3) Safety and effectiveness of Japanese herbal Kampo medicines for treatment of hyperemesis gravidarum

To investigate whether Japanese Kampo medicines, including Sho-hangekabukuryou-to, Touki-syakuyakusan, and Hange-kouboku-to, are safe for fetuses, and whether these medicines reduce hospitalizations and medical costs in pregnant women with hyperemesis gravidarum.

We used the Japan Medical Data Center database to extract data for pregnant women (aged  $\geq 19$  years) admitted to obstetric clinics or hospitals for delivery between January 1, 2005, and December 31, 2016. Eligible patients were classified into three groups: Kampo medicines for hyperemesis gravidarum, other medicines for hyperemesis gravidarum, and without hyperemesis gravidarum. Safety outcome measures were neonatal outcomes (congenital anomalies, low

birthweight, and preterm birth), and effectiveness measures were mother's unplanned hospitalization for hyperemesis gravidarum and total medical costs within 20 weeks of gestation.

We identified 121 287 eligible mothers. No significant differences in the safety measures were observed among the groups. The Kampo medication group had a significantly lower proportion of mothers with unplanned hospital admission (odds ratio 0.80, 95% confidence interval [CI] 0.69–0.92) and lower total costs (coefficient [US\$] 12.8, 95% CI –23.2 to –2.4) than the other medication group.

Kampo medicines may reduce unplanned admissions and medical costs among pregnant women with hyperemesis gravidarum

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)
- Nipro Co. Ltd, (to **Reiko Inagi**, Collaborative study on metabolome of serum exosome in HD patients)
- 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)
- 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)
- The Salt Science Research Foundation, Research Grant (to **Tsuyoshi Inoue**, Elucidation of sodium balance regulation mechanism through vagus nerve)
- Smoking Research Foundation, Project Research Grant (to **Tsuyoshi Inoue**, Mechanism of

suppression/treatment of progression of chronic kidney disease through nicotinic receptor)

- Yukiko Ishibashi Foundation, Research Grant (to **Tsuyoshi Inoue**, Elucidation of the renal protective effect mechanism of vagus nerve stimulation for chronic kidney injury)
- 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. Tsuyoshi Inoue** received the Medical Research Encouragement Prize of The Japan Medical Association.

**Dr. Hiroshi Maekawa** received the Best abstract Award at the 62<sup>nd</sup> Conference of Japanese Society of Nephrology.

**Dr. Hiroshi Maekawa** received the Best English Presentation Award at the 62<sup>nd</sup> Conference of Japanese Society of Nephrology.

**Dr. Hiroshi Maekawa** received the Best Presentation Award at the Japan Kidney Council 2019.

**Dr. Sho Hasegawa** received the CKD Award at the 8<sup>th</sup> Chronic Kidney Disease Frontier.

**Dr. Sho Hasegawa** received the YIA Award at the 56<sup>th</sup> Annual Meeting of Japanese Society of Molecular Medicine.

**Dr. Sho Hasegawa** received the YIA Award at the 10<sup>th</sup> Japanese Society of Pathophysiology in Kidney Failure.

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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 2014, we had another assistant professor, two guest researchers and two 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 Clinical Laboratory

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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 2019, 234,558 outpatient blood sampling were performed in this section. Furthermore, 266,792 urine samples were examined.

### The 2nd Section

This section deals with clinical biochemistry and immuno-serology tests. In 2019, 5,645,730 serum enzyme tests (such as AST and ALT), and 578,422 immunological tests were performed.

### The 3rd Section

This section deals with laboratory hematology and DM-related tests, and gene analysis tests. In 2019, 1,196,165 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 2019, 43,907 ECG, 27,129 pulmonary function tests, and 11,207 EEG were performed.

### The 5th Section

This section deals with ultrasonography. In 2019, 11,089 echocardiography tests, 14,325 abdominal echography tests, and 7,320 other ultrasonography tests were performed.

## Teaching activities

Lectures are given to the fourth and sixth grade medical students on clinical tests 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. 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 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, v) AI and data mining in laboratory medicine, vi) genetic testing, vii) oxidized albumin as a redox marker, viii) analysis of cardiac functions using ultrasound, ix) improvement and further clinical application of pulmonary function tests, x) elucidation of abnormality in epigenetics in cancer and its clinical application, and xi) analysis of brain function using magnetoencephalography and near-infrared spectroscopy.

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# Surgical Center

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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.

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 and 11,323 operations were performed in 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018 and 2019 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 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, micro-vascular surgery, cardiovascular surgery, minimally invasive surgery and navigation-guided orthopedic/neurosurgical surgery and stent grafting for the abdominal or thoracic aortic aneurysms. Organ transplantation and intraoperative three-dimensional echo-guided surgery are also frequently performed. Minimally invasive surgery is another recent trend of the operation. Those include endovascular treatment for heart anomalies such as ASD and VSD. More recently, the robotic surgery has started at the surgical

center.

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

## Teaching Activities

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

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

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

complicated and long operations such as transplant surgery, open-heart surgery neurosurgery and robotic surgery.

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

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

## Research Activities

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

OR

- 12) Maintenance and management of surgical equipment
- 13) Nutritional management of perioperative patients
- 14) Others

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# Department of Clinical Radiology

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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 as follows: three medical doctors, 75 radiological technicians and 1 technical official of the radiation control. The staff members of the Department of Radiology (teachers, the graduate school students, medical staffs, and the clinical trainees) join this. In addition, the doctors of other departments and the nurses cooperate and are also engaged in the 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 hospital information system (HIS) and PACS (picture archiving and communicating system). 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) Image Computing & Analysis Laboratory: The clinical section of this project is

located at the reading room in the Diagnostic Radiology Section. The main services are processing of volume image data into clinical 3D-images and analysis of imaging data. 4) Researches on new radiology techniques: Ongoing collaborative researches are as follows: image-guided radiation therapy, clinical PET, multi-detector row CT, 3-Tesla MRI, and flat panel detector.

## **Clinical activities**

### 1) Diagnostic Radiology:

The section of diagnostic radiology is responsible for all the clinical examinations of CT, MRI, and angiography/vascular interventional procedures except for cardiac and peripheral arterial studies. All of these examinations are performed under the requests of clinicians. Over two hundred CT examinations are performed using six MDCT scanners each day. Interventional procedure such as percutaneous biopsy and abscess drainage are also done by CT guidance. About seventy 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.

### 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, SPECT, and PET scans. Scanning is performed at the first basement floor in the Central Clinic Building 1. Blood flow, metabolism, and receptor functions are measured for the understanding of normal and pathophysiological states, using a variety of positron-emitter radiotracer with F-18. Whole body FDG-PET for staging of malignancy plays an important 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 with three linear accelerators, an intracavitary irradiation device (RALS), a brachytherapy, and a gamma knife for radiosurgery. The network system connecting these radiotherapy equipments, 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, which is utilized mainly for non-coplanar radiation therapy in many patients, especially with brain tumor or head and neck tumor. 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. Main supporter as the 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 2019

	Inpatient	Outpatient	Total
Radiography (plain)	97,685	80,080	177,765
Radiography (enhanced)	5,226	918	6,144
Angiography	3,343	5	3,348
Computed tomography	16,033	37,618	53,651
Magnetic resonance imaging	4,957	15,493	20,450
Nuclear medicine	1,614	2,697	4,311
Radiotherapy	5,525	8,445	13,970
Bone mineral densitometry	380	3,379	3,759

# Department of Pharmacy

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## Introduction and Organization

We have 9 faculty members, 79 pharmacy staffs, and 10 graduate students and 9 undergraduate students from the faculty of pharmaceutical sciences (as of January 1<sup>st</sup>, 2020).

## 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 (2,614 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 2019)

Number of items on in-hospital formulary: 2,614

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

out-patients	:	368,920 ps.
(outside	:	324,995 ps.)
(inside	:	43,925 ps.)
out-patient chemotherapy:		12,940 ps.

in-patients :		253,720 ps.
injection drugs	:	187,220 ps.
IVH	:	2,633 pp.
chemotherapy	:	10,485 pp.
TDM consultations (annual)	:	19,654 pp.
Numbers of hospital pharmaceutical cares (annual):		18,484 pp.

## Education

The department of pharmacy takes various responsibilities of education with regard to clinical pharmacy, pharmacology, and pharmacokinetics for students and graduate students in the faculty of medicine, in the faculty of pharmacy, and in the school of integrated health sciences. We also have our own half a year post-graduate training course optimized for new pharmacists.

For students in the faculty of medicine, we are in charge of "Pathogenetic and Pathology" as an optional course lecture. We are providing a 3-days practice course as a part of compulsory clinical practice for the M3 or M4 students and teach clinical pharmaceutics and practical knowledge of prescription and risk management to them. For the students in the health sciences and nursing, we are in charge of clinical pharmacokinetics lectures as a part of a compulsory subject, "Pharmacology and Toxicology".

For students in the faculty of pharmacy, we are in charge of lectures for the undergraduate students: "Clinical Pharmacy" (compulsory subject). They are educated for the clinical pharmacology and pharmacokinetics. For the graduate students, we are in charge of "Special Lecture Basic Pharmaceutical Science IV", "Special Lecture Clinical Science", "Advanced Course of Medical Pharmacy" as a cooperator of the Clinical Pharmacokinetics. Recent trends of the medical pharmacy as well as the practical developments and future visions of the department of pharmacy are presented in this lecture. In addition to them, we accept undergraduate and graduate students from the faculty of pharmaceutical sciences and faculty of medicine. They are doing various research activities.

Six year course education system has been launched in the field of pharmaceutical sciences since 2006. In this system, the clinical training by pharmacists at the

hospital is one of the most important curriculums. In 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 2019, 13 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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**Lecturer**

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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 30 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

## Professor

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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.

The number of devices handled in the central supply service is dramatically increasing with increased number of operations in the surgical centers.

Staffs of central supply service have also worked for re-counting of used surgical devices on surgical center floor since 2011. The work has contributed towards risk management in the hospital.

Staffs also join infection control team round and periodically count device number in each ward for appropriate management of medical devices.

## Research activities

To establish more efficient procedures for cleaning, intensive trials have been performed and the data have been presented at academic conferences. Moreover, basic research on host response to surgical insult is another theme of our division. The research is important for improving outcome of surgical patients and our data have been published as original articles

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# Division of Diagnostic Pathology

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## **Lecturer**

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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 and surgical pathology) at the University of Tokyo Hospital as well as education and research on human pathology. On May 1<sup>st</sup>, 2019, Dr. Tetsuo

Ushiku was appointed to a professorship at the Department of Pathology and Diagnostic Pathology of the University of Tokyo and continued to serve as a director of the Diagnostic Pathology Division of the hospital.

We set up Telepathology & Remote Diagnosis Promotion Center (TRDP Center) in 2013. We also started Outpatient Clinic of Pathology to provide detailed information and explanation about pathologic

diagnosis to the patients with breast cancer.

In February 2018, the University of Tokyo Hospital was selected as one of the core hospitals to promote cancer genomic medicine in Japan. From August 2018 to December 2019, the advanced medical care (category B) named 'Trial of a multiplex genomic testing by "Todai OncoPanel" for Geneprofiling of malignant solid tumors' was conducted which enrolled 200 patients. In addition, cancer panel testing covered by public health insurance (NCC OncoPanel and FoundationOne CDx) started in November 2019. We serve as members of expert panel to contribute to the promotion of genomic medicine.

We registered substantial cases of whole slide images (WSI) in the research project of Japanese Society of Pathology "Database of Pathology-WSI for Development of Artificial Intelligence (AI) Technique and AI-based Support System for Pathology Diagnosis" which was started in 2016.

## Clinical activities (diagnostic pathology and autopsy)

The annual statistics of the pathology practice in 2019 fiscal year consisted of 17,370 surgical cases, 16,216 cytology, 1,115 intraoperative histologic diagnosis, 401 intraoperative cytology, 38 autopsy cases (autopsy rate, 13.7%).

The following surgical pathology conferences are regularly held; thoracic organs (Drs. Shinozaki-Ushiku and Hinata in charge), liver and pancreatobiliary tract (Drs. Yamauchi and Tanaka), liver metastasis (Dr. Abe), and female genital tracts (Drs. Ikemura and Shintani-Domoto), breast (Dr. Ikemura, and bone and soft tissues (Drs. Ushiku and Makise). Biopsy conferences are also held in the cases of kidney (Drs. Shintani-Domoto and Hinata), and skin (Dr. Tanaka) and hematology (Dr. Shinozaki-Ushiku).

We provide FFPE specimens suitable for multiplex genomic testing with Todai OncoPanel. We also join clinicopathologic and genomic conference which is held twice a month 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. Virtual slide

scanners have been installed, which enabled us to deposit the biopsy specimens as digital information.

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 2<sup>nd</sup> grade medical students. Clinical Clerkship (CC) courses of autopsy and surgical pathology are for the 4<sup>th</sup> 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 seven junior residents (total 16 months) in 2019 for their second-year program.

## Research activities

Dr. Sasaki conducts the research to evaluate feasibility of telepathology for daily practice of diagnostic pathology. We also conduct research of developing artificial intelligence (AI)-system, such as "Development of a support tool of pathology diagnosis such as rare cancers, intraoperative report and double check using artificial intelligence (Dr. Sasaki)", and cooperate the project by "Efficiency improvement and diagnostic support of pathologic diagnosis by automatic classification of renal biopsy pathology images using Deep Learning Technology (Prof. Kazuhiko Ohe)"

The development of automatic grossing and sectioning system using AI-equipped robot is in progress as collaborative research with engineering faculty-of the University of Tokyo (Prof. Mamoru Mitsuishi) and National Institute of Advanced Industrial Science and Technology (Dr. Kiyoyuki

Chinzei, director).

We continue the study to investigate the usefulness of post-mortem CT images for hospital autopsy (Drs. Shintani-Domoto and Abe). 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.

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

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# Department of Corneal Transplantation

## Professor

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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 54 corneal surgeries including keratoplasty were

performed in 2019. 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

## Professor

Mineo Kurokawa, M.D., Ph.D. (Hematology-Oncology)

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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 100 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 2017, 17 patients (including 2 children) received autologous HSCT and 26 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  $-196^{\circ}\text{C}$  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

## Associate Professor

Yousuke Nakai, M.D., Ph.D.

## Associate

Shuntaro Yoshida, M.D., Ph.D.

**Homepage** <https://www.h.u-tokyo.ac.jp/patient/depts/kougaku/>

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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. All endoscopes in our hospital are collected in our department after use and disinfected.

## 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

	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
EGD*	10682	10556	10963	11376	11840	11740	11874	11944	11490	11699 (2177‡)
Colonoscopy	4996	5152	5208	5688	6000	6043	6394	6814	5921	5530 (109‡)
Bronchoscopy	226	255	197	196	169	218	228	362	350	316
ERCP**	959	943	1072	956	912	1035	946	1206	1137	1057
EUS†	518	551	630	698	763	766	882	1084	1023	923
Enteroscopy	181	181	282	282	375	396	310	86	304	138
Laryngoscopy	75	70	108	83	128	102	105	125	114	92
Colposcopy	307	361	378	365	404	327	295	417	430	414
Total	17944	18069	18838	19644	20591	20627	21034	22038	20769	20169

\*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

## Professor

Masaomi Nangaku, M.D., Ph.D.

## Lecturer

Daisuke Yamada, M.D., Ph.D.

Yoshifumi Hamasaki, M.D., Ph.D.

## Introduction and Organization

Hemodialysis and related blood purification therapy had been individually performed in their respective departments. However, all the departments' apparatus and human resources were centralized to form the Department of Hemodialysis and Center for Hemodialysis in 2000 at the University Hospital. The Center for Hemodialysis was further renovated and started operations in Fall of 2006. 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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# Medical Community Network and Discharge Planning Center

## Associate Professor

Masahiko Sumitani, M.D., Ph.D. (concurrently)

## 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 9 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.

# University Hospital Medical Information Network (UMIN) Center

## Professor

Takahiro Kiuchi, M.D., Ph.D.

## Associate Professor

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## Instructor

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**Homepage** <http://www.umin.ac.jp/>

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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>

SUPERCOURSE:

Online Lectures Compiled by Pittsburgh Univ., U.S.A

EPOC: Evaluation System of Postgraduate Clinical Training

Debut: Dental Training Evaluation and Tabulation System

Web-QME: Medical Education Evaluation System

ARIA: Online Recruiting System for General Use

■ Medical Examination and Treatment

<http://www.umin.ac.jp/uhosp/>

- Intoxication database
- Medical supplies and materials database
- Classification for Nursing
- Ministry of Education, Culture, Sports, Science and Technology document public information system
- National university hospital-related medical dispute report
- Lists for people and committees
- Various government official appointments, administrative websites and ML

■ General Services

(1) General information and search

- Medical / biology related websites
- Medical terminology
- A medical research organization / medical institution database

(2) Services for information providers

- Web service for public
- Web service for members
- Website preservation service

(3) Communication support

- E-mail
- Listserv
- Discussion board
- File exchange

## **Teaching Activities**

Please refer to Department of Health Communication for information about graduate and undergraduate education.

## **Research Activities**

Please refer to Department of Health Communication for information about research activities.

## **References**

Please refer to Department of Health Communication.

# Organ Transplantation Service

## Director

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The University of Tokyo Hospital has aggressively performed organ transplantation, and is one of the major organ transplant centers in Japan. In 1966, the first kidney transplantation in Japan was performed. In 1996, the first living donor liver transplantation was performed. Organ Transplant Service started to function since 2003. As for liver transplantation, till the end of 2018, 609 cases of living donor liver transplantation and 28 deceased donor liver transplantations have been performed, and the 5-year survival rate is around 85% which is much superior to the national average (~70%). The University of Tokyo Hospital has been one of the authorized institutions for heart transplantation, and lung transplantation. At the end of 2018, 111 heart transplantations and 20 lung transplantations (18 deceased donors and 2 live donors) have been performed. In addition, 77 kidney transplantations (17 deceased donors and 60 live donors) have been undergone.

In Japan, the organ transplantation is still not accepted as a common clinical practice, and the number of deceased organ donors is extremely low when compared to other developed countries. The Organ Transplant Service at the University of Tokyo Hospital integrates the heart, lung, liver, and kidney transplantation, and promotes the awareness campaign regarding the organ donation and the transplantation not only in the institution but also widely among Kanto area.

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# Department of Clinical Research Governance

## Director & Project Professor

Hideaki Ui, Ph.D.

## Research Associate

Kazuyoshi Ichihashi, Ph.D.

**Homepage** <http://www.h.u-tokyo.ac.jp/english/centers-services/organization/I4/researchgovernance.html>

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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 1<sup>st</sup>, 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 5<sup>th</sup>, November 6<sup>th</sup>, and March 12<sup>th</sup>), one Training for auditors (March 5<sup>th</sup>), 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).

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# Department of Child Psychiatry

## Associate Professor

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

## Assistant professor

Yosuke Eriguchi, M.D., Ph.D., Ayaka Ishii-Takahashi, M.D., Ph.D.

**Homepage** <http://kokoro.umin.jp/>

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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 37 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 2019, 8 psychiatrists and 6 psychologists (full-time and part-time) 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 2019 was 274, and about two thirds of the new patients consisted of patients with ASD, ADHD or tic disorders. Out of 274 patients, children of elementary school age were 125, and children of junior high school age were 41. In other words, children of elementary or junior high school age were more than half of the patients. Number of preschool children was 70, suggesting our response to increasing 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.

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, observation of assessment and treatment for follow-up patients and intervention for preschoolers, and visit to community hospital and intervention/guidance facilities for child and adolescent mental health. For general psychiatrists including senior residents of the Department of Neuropsychiatry, round for developmental disorders and an inpatient program of assessment about developmental disorders are provided as opportunity to get knowledge and experience of developmental disorders.

In response to the increasing interest to adults with developmental disorders, a seminar of developmental disorders was held in July 2019, and about 200 medical doctors, psychologists, and allied professionals attended.

## 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.

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 preliminary study of its effectiveness is undertaken.

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 as well as comparisons between patients and their healthy siblings are being conducted.

#### Genetic research

As we are interested in gene-environment interaction, we are examining influence of age of parents on emergence of ASD.

#### Neuroimaging

Studies include structural MRI, Near-Infrared Spectroscopy (NIRS) and functional MRI with exploring the pathogenesis of developmental disorders such as ASD.

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# Tissue Bank

## Director and Associate Professor

Sumihito Tamura, M.D., Ph.D. FACS

**Homepage** <https://www.h.u-tokyo.ac.jp/english/centers-services/central-clinical-facilities/tissue-bank/index.html>

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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 since 2018. Dissemination and educational activities for the advancement of tissue transplantation and transplantation medicine is our important mission.

## 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.

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# Center for Epidemiology and Preventive Medicine

## Director & Associate Professor

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## Associate & Deputy Director

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## Associates

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<https://www.todai-yobouigaku.com/>

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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. 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.

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) 2019 (from April 1, 2019 to March 31, 2020), the total number of examinees (who had basic examinations and optional examinations) was 8725 including 3161 in basic examinations, 608 in complete cardiovascular examinations, 759 in complete cerebrovascular examinations, 90 in check up for dementia, 327 in colorectal cancer screening, 651 in uterine cancer screening, 819 in breast cancer screening, 723 in lung cancer screening, 1293 in tumor marker diagnosis, 294 in estimation of gastric cancer risk, and 11 in upper gastrointestinal endoscopy (later). Check up for dementia was discontinued in December 2018.

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 2019, we issued 1330 letters of referral to other departments in our hospital and 56 to other hospitals.

We have expanded our public relations efforts and 15,000 brochures were delivered during the FY 2019.

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.

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# Department of Pain and Palliative Medicine

**Homepage** <https://www.h.u-tokyo.ac.jp/english/centers-services/central-clinical-facilities/department-of-palliative-medicine/index.html>

## History and outline of organization

About a half of the cancer patients die by cancer though of the recent innovations of anti-cancer treatments. It mainly depends on the efficacy of the first-line strategies whether cancer is curable or not. Almost all the cancer patients whose initial treatment was unsuccessful die after the distressing struggle against their disease within several years. It is clear for such patients that both sufficient anti-cancer treatments and appropriate approaches to improve their quality of life (QOL) are simultaneously indispensable.

However in our nation, most attention has been entirely paid to the improvement of cure rate and survival time of cancer patients. On the other hand, we have to consider that their QOL is scarcely concentrated until quite recently.

Palliative care means the combination of active therapeutic approach and total human care for the patients no matter which their cancer does or does not respond to anti-cancer treatments. Pain relief, other symptom management, psychological, social and spiritual cares are as a top priority for these patients. It is also emphasized that palliative care is necessary to be applied in the cancer treatment even for patients in early stage of their diseases as well as the progressive or terminal phase of their clinical courses.

In Department of Pain and Palliative Medicine of The University of Tokyo Hospital, we pain and palliative care team takes a leading role not only to control physical symptoms of cancer patients but also to care for the mental and social support at the same time, and to improve the overall QOL of patients. Moreover, we also promote the education, research and innovation of pain and palliative medicine of our hospital and university.

Palliative care is described clearly in the law "Cancer Control Act" approved by the National Diet on June 2006 that "The medical treatment to aim at relieving many kinds of pain and problems of cancer patients is applicable from the early course of the illness".

## Consultation

In The University of Tokyo Hospital, we pain and palliative care team are composed of many kinds of specialists containing three full-time staff doctors, two full-time doctors, and two certificated cancer and hospice care nurses who take an initiative in this multidisciplinary team. We visit to bedsides, consultation rooms and everywhere in the hospital, and offer palliative care to cancer patients who have received cancer care in cooperation with patients' attending doctors, ward staff, therapists of rehabilitation, social workers and every kind of professionals.

The annual number of consultation by our pain and palliative care team is getting increased. In 2019, the numbers achieved to more than total 1000 cases per year and further increased. To date we have become to collaborate with almost all departments treating cancer in our hospital. These results indicate that the hospital understands the significance of palliative care well and relies on our team.

## Education

In the Department of Pain and Palliative Medicine, junior residents of the first and second year can learn the basic knowledge and practice of palliative care by selecting an optional subject for one, two, four or eight months. And then they can participate in the pain and palliative care team and attend the daily team-conference on weekdays.

## 1) Palliative care training program

### The training course (selection) for 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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(And, 18 Japanese articles)

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# 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.

**Homepage** <http://www.h.u-tokyo.ac.jp/patient/depts/gansoudan/>

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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

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# Department of Disaster Medical Management

## Professor

Naoto Morimura, M.D.,Ph.D.

## Lecturer

Chiaki Toida M.D.,Ph.D.

**Homepage** <http://www.h.u-tokyo.ac.jp/patient/depts/dmm/index.html>

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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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2. Muguruma T, Toida C, Furugori S, Abe T, Takeuchi I. Validation of the Pediatric Physiological and Anatomical Triage Score in Injured Pediatric Patients. *Prehosp Disaster Med.* 2019 Aug;34(4):363-369.
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5. Naoto Morimura: n-hospital Medical Response to Mass Casualty Incident : Lessons Learned from Guidelines and Experiences Overseas. *The Journal of Japan Society for Clinical Anesthesia.* 2019 May 39(3):313-320.



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# International Medical Center

## Director and Associate Professor

Sumihito Tamura, M.D., Ph.D. FACS

**Homepage** <http://www.h.u-tokyo.ac.jp/english/international-patients/index.html>

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## Introduction and Organization

One of the University of Tokyo's significant challenges is globalization. The International Medical Center was established within the Central Clinical Facilities Division to enhance The University of Tokyo Hospital's development as an international medical hub. 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.

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# Department of Clinical Nutrition Therapy

## Head of the Department

Naoto Kubota (Associate Professor)

## Assistant Head of the Department

Hideaki Ijichi (Lecturer)

Rie Sekine

**Homepage** <http://www.h.u-tokyo.ac.jp/patient/depts/eiyoukanri/index.html>

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## Introduction and Organization

In 1922, a stall in the outpatient department of the hospital and hospital ward shop sold milk, baked goods, cider and ice cream. In 1925, a service contract between the hospital and the Kojinkai Foundation resulted in the start of a patient food service. In 1936, a “special therapeutic diet” approach for newborn infants, diabetes, nephropathy in which a physician prescribed the food composition individually for each patient was instituted for the first time in Japan. In 1950, a national-hospital complete food service system was announced, and the nutrient content provided was standardized. The nutrient content provision for patient meals at the time was 2400 kcal/day. In 1952, the inpatient meal service was officially outsourced to a foundation.

In 1957, the first nationwide meeting of national-university-hospital head dietitians was held at the University of Tokyo with the aim of improving patients’ diets.

In 1958, the complete food service was abolished. Implementation of a standard food service and staffing with a dietitian became required conditions, and the food service section was staffed by a part-time section chief and a dietitian. In 1962, a request from the nationwide meeting of national-university-hospital head dietitians, which primarily conducted its activities at the University of Tokyo, was realized, and the managerial dietitian system was established by a partial revision of the Nutritionists Act. In 1972, nutritional

guidance was actively provided to inpatients and outpatients with the aim of obtaining approval to charge fees, and in 1978 a medical diet charge and nutrition guidance charge were established. In 1988, a timely tray service achieved by using hot and cold food-tray carts was instituted in order to dispel the “too early, cold, unappetizing” reputation of hospital meals.

In 1991, the name of the food service section was changed to the “Department of Nutrition Management”, a change that had a long been sought by nationwide national-university-hospital managerial dietitian staff members. At the same time, the nutrition sections of the main hospital and branch hospital were consolidated, and the head of the Department of Nutrition Management, who was a managerial dietitian, assumed the section manager post to form a system composed of 5 managerial dietitians at the main hospital and 3 managerial dietitians at the branch hospital.

In 1994, as a result of a partial revision of the National Health Insurance Act, a diet therapy notification system on admission was set up. An on-admission nutrition guidance fee was also established.

In 1998, the first Diet Therapy Exhibit organized by the Department of Nutrition Management was conducted as part of the diabetes week events by the Tokyo Diabetes Association. Since then, Diet Therapy Exhibit has been conducted every year for over 20 years.

In 2001, integration of the branch hospital with the main hospital resulted in an 8-managerial- dietitian

system. In 2004, the Department of Nutrition Management was separated from the medical service division. In 2005, the introduction of the self-pay system for inpatient meals meant that inpatients began to be charged for their meals. During the same year one managerial dietitian (limited-term employment) was added to the staff.

In 2006, charges for the performance of nutrition management were newly established, and that meant providing nutrition management for all patients. The increase in work was accompanied by the addition of one managerial dietitian (limited-term employment) to the staff. Team care was introduced the same year, and in-hospital activity in the form of an all-department nutrition support team (NST) was inaugurated. Each hospital ward was staffed with a physician, managerial dietitian, and nurse in charge of an NST, and whenever necessary members from other fields (pharmacists, medical technologists, physical therapists) joined, and they held a hospital ward meeting once a week. In 2010, an NST committee was created as a result of the establishment of charges for NSTs. The NST director up until that time became a member of the committee and played an active role as the center of in-hospital NST activities. The addition of one managerial dietitian (full time) was approved as a full-time employee to engage in the activities of charges for the NST. In 2011, the inauguration of a nutritional guidance service for recipients of health checkups in the Department of Epidemiology and Preventive Medicine was accompanied by the addition of one managerial dietitian (limited-term employment) to the staff. In 2012, charges for conducting nutrition management were abolished. They were incorporated into the basic hospital-admission fee, and the nutrition management system by physicians, managerial dietitians, and nurses was improved.

In 2013, the Department of Nutrition Management was reorganized as the Department of Clinical Nutrition Therapy. A physician (Professor, the head of the Central Clinical Services Administration) assumed the concurrent post of head of the Department, and the head of the Department of Nutrition Management assumed the post of Assistant Head of the Department; they undertook responsibility for managing the food service, maintaining activities of the NST, and strengthening its functions. In 2014, two physicians,

full-time department head (associate professor) and lecturer, were assigned and improvements were made to NST activities and to the nutrition therapy, education, and research system. As a result of a managerial strategic personnel distribution, 5 new managerial dietitians (full-time) have also been assigned this fiscal year. Along with the increase in work of managerial dietitians for strengthening the nutrition management system and expanding the number of clinical trials in P1 unit, another managerial dietitian (limited-term employment) was added to the staff in May 2015.

Long-coveted introduction of the New Cook Chill System was eventually admitted by the University of Tokyo and the process was started in October 2016. Renovation of the main kitchen was started in June 2017. During the renovation, the makeshift kitchen was placed on the 1<sup>st</sup> floor (the main kitchen) and the 3<sup>rd</sup> 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.

## Clinical Activities

The Department 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 2019, individual nutritional guidance was more focused on compared to group guidance and the records show that there were 2481 instances of inpatient

nutritional guidance and 5152 instances of outpatient nutritional guidance. Especially, nutritional guidance for malignant tumor patients increased up to 501 instances. Perioperative guidance was 337 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. There were 140 guidance sessions in 2019.

In April 2014, the department started calculating charges for NST and counted 1261 instances in the first fiscal year. In 2018, according to the conditions for calculating NST charges, efforts of full-time managerial dietitians were changed and NST round twice a week. In 2019, 1044 instances were calculated, mostly adding cooperation with dentists.

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 are now screened through the common criteria in our hospital and monitored by the medical team. The high-risk patients picked up through this two-step screening are weekly referred to the NST of each floor. In April 2015, alternative initial screening criteria specific for pediatric and pregnant patients were added to the procedure manual of nutritional management, respectively. Mobile terminals specific for managerial dietitian were provided on every floor of Inpatients ward A&B, which enhanced the practice efficiency. By 2019, almost all the floor started the NST, which indicated raised awareness of nutritional care as a team medicine in our hospital.

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 accepts 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 3 to 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.

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. 102 medical students at M4 grade participated in the two-day practice course in 2019.

To disseminate NST activities fully in the hospital, the department organizes two NST-related seminars throughout the year: Basic Series for Nutrition Therapy and Clinical Nutrition Seminar. The department also organizes NST Conference and Joint Conference of Team Medicine for case discussions to facilitate cooperation with each floor NST and other medical teams. In 2015, the department started “Nutritional Management e-learning” for all employee to learn basic knowledge of nutritional management procedure. In December 2016, the exchange training program was started between the Department of Nutrition Management of The Institute of Medical Science and our department.

In October 2015, “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” was published in 2016, “The Manual of The Department of Clinical Nutrition Therapy 2017-2018” and “Records of the Kitchen Renewal” were published in 2018, “The Pocket Manual of The Department of Clinical Nutrition Therapy 2018-2021”, “New Cook Chill Manual 2018-2020” and “Illustrated Tools of Nutritional Guidance” were published in 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”
- 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<sub>R15</sub> 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.

## 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 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 and FoundationOne® CDx Cancer Genomic Profililng) were approved by PMDA in June, 2019. As well, we

provide an original multiplex genome sequencing, named "Todai OncoPanel", which is composed of DNA panel and RNA panel. The room (Room 204) is specifically allocated in the outpatient clinic for genomic medicine in cancer (twice weekly).

## Publications

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# Clinical Research Promotion Center

## **Professor, Director**

Takashi Moritoyo M.D., Ph.D.

## **Associate Professor, Vice Director**

Chie Sakanaka, M.D., Ph.D. (until July), Tatsuya Maruyama, M.D., Ph.D. (from August)

## **Project Lecturer**

Kosuke Kashiwabara, Ph.D.

## **Assistant Professor**

Yukari Uemura, Ph.D. (until May), Gaku Oguri, M.D., Ph.D.,

Takuya Kawahara, Ph.D., Mihoko Shibuya, M.D., Ph.D. (from June)

## **Project Assistant Professor**

Keiko Ueda, M.D., Ph.D., Mariko Inoue, M.D., Ph.D.

**Homepage** <https://www.h.u-tokyo.ac.jp/english/centers-services/central-clinical-facilities/clinical-research-support-center/index.html>

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## **History and Organization**

The Clinical Research Support Center was established in 2010. 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.

The Center was selected in 2011 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 clinical research functions 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 Center responsible for conducting quality assurance audits. Also, with the aim to improve 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 supervision and monitoring system in the departments.

In April 2016, we transferred ethical review process of specific clinical trials (involving invasion and intervention) 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 secretarial and administrative duties, center will continue to take responsibilities.

Moreover, a 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. Since then our hospital has been functioning as a

core clinical research hospital in Japan.

Based on the enforcement of the Act on 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 duties.

In addition, in order to strengthen the functions involved widely by the Clinical Research Support Center, in 2015, we established 3 new divisions outside the unit, Education and Training Division, Clinical Trial Implementation Division and University Hospital Network Promotion Division. In fiscal year 2017, we further integrated safety information functions of the Site Coordinating Unit and the Central Coordinating Unit and set it as 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 move outside the unit. Regulatory Strategy Division was also established in the Central Coordinating Unit in 2017.

In order to strengthen governance and functionality within the center, Central Clinical Research Manager and Advanced Medical Care Program Manager were placed to ensure that the clinical research are implementation appropriately by collaborating with the Department of Clinical Research Governance. We established Clinical Research Site Secretariat, enacted general and individual rules to respond to the Clinical Trials Act enforced in April 2018.

In December 2019, the center was renamed as Clinical Research Promotion Center to clarify that it is an organization that will further advance clinical research. The Clinical Research Promotion Center was reorganized by 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 Hospitals 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 Support Activities**

The duties of the Center range from serving as the secretariat for the IRB to supporting the implementation and reporting of clinical trials.

#### **<Site Coordinating Unit>**

In 2004, the Site Coordinating Unit began providing assistance for investigator-initiated clinical trials evaluating therapeutic drugs and studies involving unapproved drugs in addition to conventional clinical trials (use of unapproved drugs in clinical research was shifted to Research Ethics Committee of Graduate School of Medicine and School of Medicine in 2015. In 2018, it was moved to Evaluation Committee on Unapproved News Drugs). To further improve the quality of these research we decided to adopt ICH-GCP guidance and complied with the following guidelines, procedure manuals, styles and guidance etc.

- 1) Guidelines for investigator-initiated study and use of unapproved drugs in clinical research.  
(Guidelines for implementing specified clinical trial, as of April 2016)
- 2) Procedures for conducting investigator-initiated clinical study and use of unapproved drugs in clinical research.  
(Procedure manual for implementing specific clinical trial, as of April 2016)
- 3) Guidance for writing research protocol for voluntary clinical research.  
(Guidance for writing research protocol for specific clinical trial, as of April 2016)

- 4) Guidance for writing informed consent for voluntary clinical research.

(Guidance for writing informed consent for specific clinical research, as of April 2016)

- 5) Handling guidelines for financial burden on patients participating in investigator-initiated trials and clinical research.

From 2009, we have been providing support for all invasive and interventional clinical research.

For secure process of the applications of industry-sponsored clinical trials to IRB, we hold preliminary hearing system (named as "protocol presentation") before IRB. As a result, we could avoid re-examination of research.

Clinical research coordinators (CRC) of the Center have been supporting all clinical trials for approval and post marketing research since 2002. We started supporting in part investigator-initiated research in 2004. In 2005 we started providing CRC support to investigator-initiated research on a beneficiary-pays basis, and clinical pharmacology studies in healthy volunteers in 2012. CRCs exclusively involved in investigator-initiated research, have been employed as needed. CRC support for Advanced Medical Care Program B which Tokyo University Hospital participated as a head investigational site was initiated in 2017.

As part of patient awareness campaign, we continued updating the Center website, prepared leaflets and distributed them at outpatient receptions. The leaflets contain information about research currently recruiting participants. CRCs 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.

#### <Central Coordinating Unit>

Central Coordinating Unit, established in 2010, has been implementing the system successively partly supported by the MHLW-funded Early-Stage and Exploratory Clinical Trial Project.

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 at the central coordinating unit, starting from May 2015. Moreover, since clinical departments were placed in charge of monitoring and data management of all exploratory studies, and the center undertook responsibility for supervision of the quality control (QC). 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 approved marketing in June 18, 2015.

#### < Safety Information Management Division >

This division manages SAE (severe adverse event) reporting and supports various safety reporting in order to ensure that clinical studies are conducted safely.

#### <P1 Unit>

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 we move to new ward with augmented 30 beds (one room for 15 beds, three rooms for 5beds) exclusively aimed for clinical trial on the 12th floor of the inpatients' ward B 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.

From April 2014 on, as a second phase of the project, we developed a system to strengthen cooperation in clinical research education and training and development of seeds. As part of the Alliance activities the University of Tokyo developed a clinical research support system UHCT ACRess jointly with Fujitsu in 2011, to support clinical researchers in the quality and project management. UHCT ACRess can easily be customized by researchers. Currently, we are expanding the use to researchers other than Alliance members.

We have also 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 have been taken over by the Alliance Office (located within the University of Tokyo) from the preparatory meeting in July 2012. The initiative considered to share education curriculum as one of the common educational programs of national university hospitals nationwide. 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 in order to support and promote 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 became mandatory in 2013. In addition, resident physicians underwent one-month training at the Center, as a part of the M.D. residency-training program. Starting in 2017, we have been offering systematic lectures on

"Clinical Research" for M2 medical students.

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 the University Hospital Clinical Trial Alliance or (UHCT Alliance).

In 2015, we introduced clinical instructor system in which physicians from clinical departments concurrently serve as a clinical instructor, 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. In addition, we held a joint workshop series with 8 alliance universities in the Kanto Koushinetsu area. Since 2017, Japan Agency for Medical Research and Development (AMED) sponsored training workshop for clinical research personnel has been held at the University of Tokyo.

Furthermore, in response to the shortage of biostatisticians, biostatistics and bioinformatics course was established by AMED, at the university hospital. Master's course starting in FY2018 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 2019, the Center was involved in scientific meetings, which include The Japan Society of Clinical Pharmacology and Therapeutics, Conference on CRC and Clinical Research, etc. 19 publications and academic papers etc. (English papers 17, Japanese papers 2) were produced.

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# Division of Tissue Engineering

## Director & Professor

Kazuto Hoshi, M.D., Ph.D.

## Vice Director

Atsuhiko Hikita, M.D., Ph.D.

## Project Associate Professors

Atsuhiko Hikita, M.D., Ph.D., Fumiko Yano, D.D.S., Ph.D.

## Project Lecturer

Ysunori Omata, M.D. Ph.D.

## Research Associates

Yukiyo Asawa, D.V.M., Ph.D., Makoto Komura, M.D., Ph.D.,

Ryota Chijimatsu, Ph.D.

**Homepage** [http:// square.umin.ac.jp/t-e/](http://square.umin.ac.jp/t-e/)

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## Introduction and Organization

Division of Tissue Engineering was established as a special medical office in The University of Tokyo Hospital, in October 2001 and has a fully equipped 800 m<sup>2</sup> 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, 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.

## 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 aim 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 are conducting 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. Based on the findings and knowledge gained through our clinical study “Development of implant-type tissue-engineered cartilage for patients with nasal deformity in cleft lip and palate” conducted previously, we carried out 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”. Another investigator-initiated clinical trial applying implant-type tissue-engineered cartilage for the treatment of tracheal stenosis has also been started. In addition, we are preparing for a clinical study of treatment for temporomandibular joint disorder taking

advantage of anti-inflammatory and tissue repairing abilities of adipose stem cells.

In the laboratory for pediatric regenerative medicine, we are doing research to fabricate an engineered airway by tissue engineering technique to fabricate generic technology for clinical study. In addition, fundamental researches to perform a clinical study of the cytokine therapy for the trachea malacia are carried out.

## 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. 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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### 【著書】

# 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

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## 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 554.4m<sup>2</sup> 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 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.

## 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.

**Laboratory of Cavitation & Lithotripsy**

*Department of Urology, Faculty of Medicine*  
*Department of Mechanical Engineering, School of Engineering*

Development of a new method of lithotripsy using high intensity focused ultrasound induced cavitation.

**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.

**Division of Neutron Capture Therapy & Immunotherapy for Cancer**

*Department of Cardiothoracic Surgery, Graduate / School of Medicine*  
*Department of Radiology, University of Tokyo Hospital*  
*Department of Nuclear Engineering and Management, School of Engineering*

*Endowment Department, Department of Immunotherapeutics (Medinet)*

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 immunotherapeutic approaches. We develop the tumour specific drug delivery systems entrapped boron or gadolinium compounds as neutron capture agents.

**Development of new method of detecting and imaging chemical probes for biomolecules**

*Laboratory of Chemistry and Biology,*  
*Graduate School of Pharmaceutical Sciences*  
*Department of Cardiovascular Medicine*

To develop chemical probes for imaging of biomolecules. To visualize arteriosclerotic and ischemic lesions by using fluorescent probes and MRI contrast media.

**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 "virusmimicking" 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.

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## 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.

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**Center for Disease Biology and  
Integrative Medicine**

# Laboratory of Molecular Biomedicine for Pathogenesis

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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

### Laboratory for New Generation Drug Discovery

This endowed laboratory was established in 2017 for the purpose of the drug development aiming at the clinical application of AIM protein and related materials. In this laboratory, we investigate the process development for the AIM protein manufacturing under the GMP condition. In addition, we are trying to find small molecules that can activate AIM through developing the high throughput screening

system and the structural analysis of AIM. This laboratory is coming to completion this 3<sup>rd</sup> year.

### Joint Meeting

In July 2019, several medical laboratories from Shimane University and our laboratory jointly held the 4<sup>th</sup> summer seminar in Tsuwano, Shimane. The members from the both universities including the teaching staffs, graduate students and researchers, fully enjoyed this work shop, and having intense research sessions with lively discussions, which can lead to future collaborations. We could also strike up a friendship through the dinners and recreations during the three days.

Similar meetings are organized by our laboratory every year, *e.g.* Taiwan-Japan Joint Meeting in 2013 (hosted by National Taiwan University, National Yang Ming University, and the University of Tokyo), the CREST joint meetings in 2014 and 2015 (hosted by Kumamoto University and the University of Tokyo) and, Scientific Meeting in 2016 and 2018 (hosted by Shimane University and the University of Tokyo) and, Taiwan-Japan Joint Meeting in 2017 (hosted by National Taiwan University and the University of Tokyo). We will keep planning such Joint Meetings in the future.

### Seminar hosted by our lab

Title: Study of the involvement of MIC in the pathological regulation of autoimmune diseases by AIM. / Prof. Seiamak Bahram (University of Strasbourg, France)

In January 2020, we organized an invited lecture by Prof. Seiamak Bahram. He introduced his research regarding MHC class I-related sequence (MIC) gene.

## Publications

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# Laboratory of Structural Physiology

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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 2018.10, 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), Makiko Negishi (Research Associate), Kazuhiko Ishii (Research Associate), Kenji Yamagushi (Project Researcher), Hasan Ucar (Project Researcher), Yusuke Iino (Doctor course student D4), Mio Tajiri (Doctor course student D3), Takeshi Sawada (D3), Yuichi Morimoto (D3), Toshiaki Kume (D2), Hongyu Amy Chang (Master course student, M1), Hitoshi Okazaki (Medical Intern), Monami Nishio (Medical school

student, M1), 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 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).

Dendritic spines can change their forms also with day-by-day fluctuations of the sizes of postsynaptic densities (Yasumatsu, Ksai J. Neurosci 2008). Such spontaneous fluctuations are slow, but happening continuously, and play a determinant role in determining the spine size (distribution), and spine elimination and generation. These dynamics are important for the brain function in health and disorders. In fact, calcineurin is required for long-term depression and activity-dependent spine shrinkage, and calcineurin mutations have been identified in patients with schizophrenia. Moreover, mice with conditional knockout of calcineurin B (CNB-KO) exhibit behavioral abnormalities suggestive of schizophrenia. Changes in the dendritic spines of these mice, however, have not been investigated. We therefore examined the dendritic spines of CNB-KO mice, and observed a significant reduction in small spines and an increase in large spines in the prefrontal and visual cortices of CNB-KO mice. The effect of CNB-KO on the spine sizes was relatively moderate, possibly due to the presence of spontaneous fluctuations of dendritic spines. Thus, CNB-KO mice showed the spine phenotype similar to those recently reported in patients with schizophrenia (Okazaki, Kasai, Neurosci. Lett, 2018, Ref. 1).

In this year, we revealed that the fluctuations have a stabilized role in recurrently connected neural network with Hebbian learning rule, which tends to show runaway activities. This was diminished by the fluctuations, and the spine volume distributions were unimodal as we found in vivo. Despite the fluctuations, the circuits can store memory due to the plasticity induced by the spontaneous activity using simulation with large scale neural network (Humble, 2019, Ref. 3). Using AS probe, we have demonstrated that the long-term ketamine effects on depressive symptoms were due to spine generation in the prefrontal cortex (Mod-Sada, 2019, Ref. 1). Two-photon glutamate uncaging is the most method to investigate spine enlargement, but never been introduced in vivo neocortex. We have developed a method to apply two-photon uncaging in vivo, and found that spine

enlargement can be induced also in neocortex but only 20% population of spines. In contrast, we were successful in inducing spine shrinkage in most spines as in hippocampus, indicating that the selective induction of spine enlargement is not due to technical issue, while spines in neocortex are selected for enlargement (Noguchi, 2019, Ref.4). This property of neocortical spine may act to reduce overwriting, and the mechanisms of selection should be investigated in the future.

(2) The presynaptic functions:

We have established a new imaging approach to monitor presynaptic function using the presynaptic proteins called SNARs which mediate exocytosis by their assembly and a fluorescent life-time imaging to monitor FRET between the two SNAREs spanning the two membranes (VAMP2 and Syntaxin1, Takahashi, Kasai, Nat. Commun. 2015). We are now applying this technique to investigate the interaction of pre- and postsynaptic parts of synapses in a single identified spine synapses. We have obtained the preliminary data showing the effects of spine enlargement on its presynaptic terminals.

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# Laboratory of Biomedical Equipment and Biomaterials

## Associate Professor

Taichi Ito, Ph.D.

## Assistant Professor

Naoki Tomii, Ph.D., Seiichi Ohta, Ph.D.

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## Introduction and Organization

The Division tightly collaborates with Faculty of Engineering. Prof. Ito charged at Department of Chemical System Engineering and Bioengineering. The current laboratory members include Assistant Professor Ohta, one postdoc, three associates, and 16 graduate students School of Engineering and Medicine.

## Teaching activities

Associate Prof. Ito is 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.

## 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, Assistant Professor Tomii and his students are developing an advanced imaging system

using ultrasound with large interaction and low invasiveness with the living body, minimally invasive treatment using ultrasound, and a combination device with drugs.

### 1. Ultrasonic imaging

#### An ultrasonic CT (Computed Tomography)

We are developing clinical testing equipment for ultrasonic CT screening and diagnosis system aiming at the early detection of breast cancer. Ultrasound CT uses ultrasound which is minimally invasive and has many interactions with the living body (large amount of information that can be acquired) as the imaging method. The amount of obtained information is large in proportion to the computation cost. We are developing high precision image reconstruction algorithm utilizing parallel computing and application technology extracting new biological information.

### 2. Ultrasound therapy

#### 1) Development of minimally invasive treatment equipment and systems

We are developing an intracranial ultrasonic irradiation system and conduct research aiming to induce action potential and stimulated motion by adding mechanical stimulus to nerve cells. In addition, we are also developing therapy monitoring method aiming at high accuracy of minimally invasive treatment.

#### 2) Ultrasonic drug delivery system

We are also developing ultrasonic drug delivery as a therapeutic application of ultrasound. In particular, we aim to realize the enhancement of drug permeability of the cerebrovascular barrier by combining ultrasound and microbubbles.

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# Laboratory of Clinical Biotechnology

## Professor

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

## Associate Professor

Shinsuke Ohba, D.D.S., Ph.D. (by April 2019), Hironori Hojo, Ph.D. (from October 2019)

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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). 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). We are 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.

We have also worked on the development of direct reprogramming methods in which osteoblasts and chondrocytes are directly generated from somatic cells including fibroblasts, without the use of stem

cells (*Arthritis & Rheumatology* 50:3561, 2004; *FASEB Journal* 21:1777, 2007).

## 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 Communica-*

tions 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 Associate 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). The high-performance hydrogel unit would integrate signaling factors with shape-controlled scaffold materials, leading to the development of implant devices that work as scaffolds for tissue repair and also as carriers of bioactive factors. Through a series of these studies, we are aiming to create a "four-dimensional scaffold system" that achieves efficient tissue regeneration by controlling cell proliferation and differentiation in temporal and spatial manners. The system will not only be applicable to the regeneration of other tissues; it will also contribute to the development of basic technologies for the temporal-spatial control of *in situ* tissue formation, which is versatile in the prevention, diagnosis, and treatment of various diseases.

## Publications

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4. Fujinaga I, Yasuda T, Asai M, Chung UI, Katashima T, T. Sakai. Cluster growth in percolation process from diluted system. *Polymer Journal* 2019;52:289–297
  5. Katashima T, Chung UI, and Sakai T. Mechanical Properties of Doubly Crosslinked Gels. *Polymer Journal*, 2019;51:851-859
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# Laboratory of Microenvironmental and Metabolic Health Sciences

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## Introduction

Laboratory of Environmental Health Sciences of the Center for Disease Biology and Integrative Medicine moved the laboratory from the 3rd floor of the Medical Faculty of Medicine Building 1 to the 8<sup>th</sup> 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 (three for the doctoral course and three for the master course), three external researchers, and one research assistant conducted the researches together during the year of 2019.

This laboratory belongs to the Department of Social Medicine, cooperates to the Departments International Health Sciences and Social Public Health, and is engaged in education and research on relationships. The laboratory is also associated with the Department of Cellular Signaling, the Molecular Cell Biology.

## Research activities

Laboratory of Microenvironmental and Metabolic Health Sciences was constituted by two major research projects; “lipid biology” by a group of Murakami (professor) and “environmental toxicology” by a group of Ohsako (associate professor).

### 1. Lipid biology (Murakami’s group)

The main theme of this research project is to clarify the role of lipids in health and diseases. Lipids supply the largest source of energy in living organisms, are main components of cell membranes, act as signal molecules, and constitute a barrier covering the body surface (four major functions of lipids). Lipids are environmental nutritional factors ingested from foods, as well as tissue microenvironmental regulators that spatiotemporally coordinate various biological responses after being metabolized to specific bioactive lipids. By performing comprehensive lipid analysis (lipidomics) on gene-manipulated mice for lipid-metabolizing enzymes, particularly those in the phospholipase A<sub>2</sub> (PLA<sub>2</sub>) 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

Polyunsaturated fatty acids (PUFAs) confer health benefits by preventing inflammation and obesity and by increasing thermogenesis in brown and beige adipocytes. As well as being supplied exogenously as nutrients, PUFAs are largely stored in membrane glycerophospholipids and released by phospholipase A<sub>2</sub>s (PLA<sub>2</sub>s). However, the molecular identity of the PLA<sub>2</sub> subtype(s) that supplies endogenous PUFAs for metabolic homeostasis remains unclear. PLA2G2D, a secreted phospholipase A<sub>2</sub> (sPLA<sub>2</sub>) isoform, is constitutively expressed in M2 macrophages in white adipose tissue (WAT) and shows a reciprocal correlation with obesity. Studies using global and macrophage-specific *Pla2g2d*<sup>-/-</sup> mice have revealed that PLA2G2D ameliorates diet-induced obesity and insulin resistance and counteracts the proinflammatory M1 macrophage bias in WAT. Moreover, PLA2G2D increases energy expenditure and thermogenesis by promoting WAT browning. Mechanistically, PLA2G2D constitutively supplies a pool of PUFAs, ω<sub>3</sub> in particular, in WAT. These results underscore the contribution of the M2 macrophage-driven PLA2G2D-PUFA axis to metabolic health (Sato et al, *Cell Reports* 2020).

Choline supplies methyl groups for regeneration of methionine and the universal methyl donor *S*-adenosylmethionine (SAM) in the liver. Although phosphatidylcholine (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 conversion of lysophosphatidylcholine 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, and reduced fat mass with adipocyte browning. Accordingly, mutant mice are lean, display growth retardation, and die prematurely. Thus, the

methyl group flux from choline endogenously generated through PC breakdown by the PNPLA7 axis is essential for liver functions and systemic energy homeostasis (manuscript in preparation).

### 2) Cardiovascular diseases

Aortic dissection is a life-threatening aortopathy involving separation of the aortic wall, yet the underlying mechanisms are still incompletely understood. Epidemiological evidence suggests the beneficial effects of unsaturated fatty acids on cardiovascular health. Here we show that PLA2G5, a sPLA<sub>2</sub> isoform expressed in aortic endothelial cells, plays a protective role against aortic dissection by endogenously mobilizing vasoprotective lipids. Global and endothelial cell-specific *Pla2g5*-deficient mice frequently develop aortic dissection shortly after infusion of angiotensin II (AT-II). In the AT-II-treated aorta, endothelial PLA2G5 mobilizes oleic and linoleic acids, which attenuate ER stress, increase the expression of lysyl oxidase, and thereby stabilize the extracellular matrix in the aorta. The increased susceptibility of *Pla2g5*<sup>-/-</sup> mice to aortic dissection was rescued by dietary supplementation with oleic or linoleic acid. These findings reveal an unexplored functional link between sPLA<sub>2</sub>-driven phospholipid metabolism and aortic stability, possibly contributing to the development of novel diagnostic and/or therapeutic strategies for aortic dissection (Watanabe et al, *J Biol Chem* 2020; selected as an Editors' Pick).

### 3) Skin diseases

Lipids play crucial roles in skin homeostasis and diseases. We have currently reported that PLA2G2F, an epidermal sPLA<sub>2</sub>, 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 iPLA<sub>2</sub> 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 PLA<sub>2</sub> knockout strains, as well as by gene expression profiling of PLA<sub>2</sub>-related genes in mouse and human skins, we have identified several PLA<sub>2</sub>s that appear to be linked to skin diseases. Of

these, we found that PLA2G4E (cPLA<sub>2</sub>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 lipid mediator *N*-acylethanolamine (NAE) that has an anti-inflammatory function. *Pla2g4e* deficiency lead to 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. This is the first demonstration of the biological role of PLA2G4E as an *N*-acyltransferase *in vivo* (manuscript in preparation).

#### 4) Allergic diseases

We have currently shown that PLA2G3, an sPLA<sub>2</sub> isoform secreted from mast cells, promotes mast cell maturation by driving the paracrine PGD<sub>2</sub> circuit in cooperation with microenvironmental fibroblasts (Taketomi et al, *Nat Immunol* 2013) and that PAF-AH2, a unique PLA<sub>2</sub> that hydrolyzes oxidized phospholipids, ensures optimal mast cell activation and thereby allergic responses through producing unique EPA/DHA metabolites (ω3 epoxides) (Shimanaka et al, *Nat Med* 2017). We are now analyzing other PLA<sub>2</sub> knockout strains that have alterations in allergic responses.

#### 5) Neuronal diseases

Mutations in the *PLA2G6* gene, which encodes PLA2G6 or iPLA<sub>2</sub>β, are responsible for *PARK14*-linked Parkinson's disease with α-synucleinopathy. However, it is unclear how *PLA2G6* mutations lead to α-synuclein (α-Syn) aggregation and dopaminergic (DA) neurodegeneration. We found that *PLA2G6*-deficient *Drosophila* exhibits the degeneration of DA neurons, leading to defects in neurotransmission and motor ability. Lipidomics analysis of the brain reveals that the acyl-chain length of phospholipids is shortened by *PLA2G6* loss, which causes membrane lipid disequilibrium-induced ER stress. Introduction of wild-type human PLA2G6 or C19orf12, an orphan protein residing in the mitochondria-ER contact site, in *PLA2G6*-deficient flies rescues the phenotypes associated with altered lipid composition, ER stress and DA neurodegeneration, whereas that of a disease-associated missense mutant, PLA2G6 A80T, fails to suppress these phenotypes. The acceleration of α-Syn

aggregation by *PLA2G6* loss or A80T expression is suppressed by the administration of linoleic acid, which corrects lipid composition in the brain. These results suggest that membrane remodeling by PLA2G6 is required for the survival of DA neurons and α-Syn stability (Mori et al, *PNAS* 2019).

## 2. Environmental Toxicology (Ohsako's group)

Ohsako's group is studying various themes related to the environmental issues from the point of view of social medicine. This year one paper was published as showed below, and one project is still going on. 1) Analysis method of the effect of environmental toxic substances by an *in vitro* test system using human ES cells: Human ES cells have an *in vitro* test system that mimics an experiment of exposure to environmental chemicals to a fetus that can never be performed in humans. We devised a new method by utilizing the process of differentiation into nerve cells, and summarized the report of the experiment that was once performed with the dioxin exposure model (Sarma et al., 2019). 2) Regarding the physiological function of the aryl hydrocarbon receptor (Ahr): A new phenotype was accidentally discovered in the course of a project using Ahr-deficient mice (Ahr-KO), which has long been known for its environmental toxicity.

### 1) Effect of environmentally toxic substances by *in vitro* test system using human ES cells

After maintaining and culturing human ES cells and proliferating in large quantities, MEF used as feeder cells was removed by about 80% with unit gravity, and EB was seeded on a 96-well multi-plate with a low-adhesive round bottom at 9000 / well. It was formed for 7 days. Then, the EBs were transferred to a matrix coat dish to cause outgrowth, and the cells were cultured until a neural rosette was confirmed. After replating, when a large number of cells with MAP2-positive neurites were differentiated, TH, MAP2, and Hoechst were stained and image analysis was performed. The results showed that TCDD used for exposure unexpectedly increased the incidence of TH-positive cells (Sarma et al., *IJMS* 2019).

### 2) Physiological function of Ahr

A new phenotype was unexpectedly found in the course of a project using AhrKO, which has long been known for environmental toxicology study. Phenotypes such as liver fibrosis, decreased fertility, and immune

system abnormalities have been reported in AhrKO mice. On the other hand, endogenous ligands for Ahr include the tryptophan metabolite FICZ and ITE produced by the intestinal flora, and Ahr regulates Th17/Treg differentiation in association with these ligands and is involved in autoimmune diseases. At 10 weeks of age, loose stools and melena were observed only in AhrKO, followed by clear rectal prolapse. Compared to the wild type, AhrKO mice showed hypertrophy of the spleen and mesenteric lymph nodes, thickening of the colon and marked inflammatory cell infiltration of the lamina propria. CD4+IL17+IFN $\gamma$ -Th17 cells were increased significantly in the spleen, mesenteric lymph nodes, and colonic lamina propria, whereas there was no difference in CD4+Foxp3+Treg cells. Previous reports have reported that Th17 differentiation is suppressed in spleen cells of Ahr-deficient mice, which is different from this finding. In addition, liver fibrosis did not cause clear lesions. Metagenomic analysis of the contents of the large intestine revealed a facility-specific flora. The AhrKO phenotype we discovered here indicates that Ahr dysfunction in inflammatory bowel disease and changes in the intestinal flora that produce Ahr endogenous ligands are involved in pathogenesis.

## 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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# Laboratory of Animal Resources

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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 4 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 885 at the end of academic year 2019.

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 5 mutant marmosets which carried mutations in coding region of *FMR1* gene.

### 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. This result indicates a functional redundancy between mGluR1 and mGluR5 in cerebellar Purkinje cells.

### 3. Generation of 22q11.2 DS syndrome model mouse

22q11.2 deletion syndrome (22q11.2DS) is a genetic syndrome caused by a heterozygous deletion of chromosomal region 22q11.2. Most patients have a deletion of 3 Mb in this region, whereas some patients have smaller deletions of 1.5 Mb or 1.4 Mb. Genes of human chromosome 22q11.2 have been highly conserved in mouse chromosome 16qA13. This syndrome has been shown to increase the risk of developing schizophrenia, intellectual disability,

autism spectrum disorders and other psychiatric disorders. Particularly, about 30% of patients with this syndrome develop schizophrenia. We have successfully generated mice with 3 Mb deletion (*Del(3Mb)/+*) by genome editing techniques using CRISPR/Cas9 system. *Del(3Mb)/+* mice showed reduction of auditory prepulse inhibition and hypoactivity in the open field test. Furthermore, we have generated two model mice with 1.5 Mb deletion (*Del(1.5Mb)/+*) and 1.4 Mb deletion (*Del(1.4Mb)/+*) by genome editing. *Del(1.4Mb)/+* mice displayed decreased locomotor activity, which possibly reproduces the negative symptoms of schizophrenia, and *Del(1.5Mb)/+* mice showed reduction of prepulse inhibition and impairment of contextual- and cued-dependent fear memory.

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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 $\alpha$  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 2019, we took charge of lectures: "Description and Processing of Medical Knowledge" in the 2-year master course in the Medical Science Graduate Program, "Computer Processing of Medical knowledge and AI application" in School of Public Health course, and "AI in Medicine" in the GCL Special Lecture III.

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. Two students in the doctor's program, two students in the master's program are enrolled in our laboratory in FY2019. Additionally, five undergraduate students took practice education in our laboratory through M3 Elective Clerkship program.

## 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. 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. In future, we plan to achieve the social implementation of the support 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)**

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# Department of Medical Education Studies

## Professor

Masato Eto, M.D., Ph.D.

## Lecturer

Daisuke Son, M.D., Ph.D.

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## History 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 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 evidences 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 Its 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 member(s) 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.

# Department of International Cooperation for Medical Education

## Lecturer

Hiroataka Onishi, M.D., M.H.P.E., Ph.D.

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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, multiple 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

## **Director, Professor**

Hiromi Sanada, R.N., P.H.N., W.O.C.N., Ph.D.

## **Vice Director, Professor**

Kiyoko Kamibeppu, R.N., P.H.N., Ph.D.

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

## **Project Associate Professor**

Makoto Oe, R.N., P.H.N., Ph.D.

## **Project Assistant Professor**

Hiromi Tobe, R.N., P.H.N., Ph.D.

## **Project Researcher**

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

**Homepage** <http://gnrc.m.u-tokyo.ac.jp/en/>

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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 environ-

ment 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 2019, three international joint research projects and an industry-government-academia research projects were undertaken. In addition, two patent applications were submitted, and 32 original English articles were published.

## **Executing Innovative Research**

### **1. International Invited Faculty**

In 2019, we invited two researchers: Prof. Joan E. Haase: Holmquist Professor in Pediatric Oncology Nursing, Indiana University, 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 2019, two PD researchers participated in this program, and completed the program.

### **3. Other Universities’ Young Researchers**

In 2019, our PD seminars were opened to young researchers from other universities, and by the end of the year, a total of 288 researchers attended. Furthermore, we conducted research consultations or technical assistance and training for five of these young researchers.

We held an international summer program, and 20 young researchers attended it from four countries.

## **Building Future Research**

### **1. Global Nursing Research Center Fund**

The Global Nursing Research Center Fund was continued for the purpose of fostering young researchers.

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# Office of International Academic Affairs

## Head

Yasuyuki Seto

## Assistant Professors

Joseph Green

Keiko Nanishi

Yosuke Matsumiya

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

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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 2019 academic year (April 1, 2019 through March 31, 2020).

### 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, this year's 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, and ten students were trained at the hospital in 2019-20: three from Ludwig Maximilian University of Munich, one from Imperial College London, two from Peking University, two from National Taiwan University, and two from University of Cagliari, in Italy. However, the pandemic forced two students to cancel elective clerkships scheduled in March 2020.

#### 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.

The University of Tokyo Faculty of Medicine has agreements for exchange programs—for 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, and Ludwig Maximilian University of Munich. The OIAA nominates qualified

students for each university and assists in their preparation for study abroad. During April through July 2019, one student studied at the University of Pennsylvania, two at Johns Hopkins University, two at the University of Michigan, three at National Taiwan University, two at National University of Singapore, and one at Ludwig Maximilian University of Munich. In addition, in collaboration with the University of Tokyo International Research Center for Neurointelligence, the OIAA sent four researchers to Harvard University for one to two months of research study during April through July 2019.

Among universities and organizations with which the Faculty of Medicine does not have an exchange agreement, the OIAA provided support for one clinical internship at Harvard University, one clinical internship at Mahidol University, one clinical internship at Thammasat University, two internships in international community health in Cambodia, and one clinical internship at the University of Toronto.

### 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 2019-20, the OIAA assisted in preparing Medical Student Performance Evaluations for two applicants.

## 2. International Academic and Research

### Agreements

During the 2019-20 academic year, the OIAA renewed a Faculty of Medicine agreement with the University of Pennsylvania, a Faculty of Medicine memorandum of understanding with the University of Hawaii, and a university-wide agreement with the University of Gothenburg.

## 3. Education and Research Activities

Dr. Yosuke Matsumiya supervised and taught the courses Medical English I/II and trained undergraduate students, graduate students, and faculty in English oral presentation skills.

Dr. Keiko Nanishi taught the course, "Basic Tools for Population/Public Health Research," and offered classes in the School of International Health, where she and Dr. Joseph Green supervised graduate

students and conducted research on international health.

## Publications

1. Okawa S, Gyapong M, Leslie H, Shibamura A, Kikuchi K, Yeji F, Tawiah C, Addei S, Nanishi K, Oduro AR, Owusu-Agyei S, Ansah E, Asare GQ, Yasuoka J, Hodgson A, Jimba M; Ghana EMBRACE Implementation Research Project Team. Effect of continuum-of-care intervention package on improving contacts and quality of maternal and newborn healthcare in Ghana: a cluster randomised controlled trial. *BMJ Open*. 2019 Sep 11;9(9):e025347.
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# MD Scientist Training Program

## Professor and Director

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

## Assistant Professor

Yuki Sugaya, M.D., Ph.D.

Kei Takahashi, Ph.D.

**Homepage** <http://www.ut-mdres.umin.jp/> (in Japanese)

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## 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 two assistant professors Yuki Sugaya and Kei Takahashi, 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 more than 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. In FY2019, a total of 8 students received the Program's support for carrying out basic medical research abroad and to present their research achievements at international scientific meetings. Unfortunately, 5 other students had to cancel the research abroad in March because of the COVID-19 pandemic. We also support exposure to clinical training in foreign hospitals with the Osamu Otsubo Tetsumon Fellowship, however, a total of 14 fellows canceled the clinical training in foreign hospitals and studied cutting-edge medical care in domestic hospitals instead.

### 2) Organizing an MD scientist training program retreat

A MDSTP retreat was held on February, 15-16, 2020 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. In 2019, the joint retreat was held in Nagoya, 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. In 2019, this was held on August, 17-18 at the Tetsumon memorial hole in the University of Tokyo. More than 70 people participated in the retreat and presented their ongoing research progress and future plans.

## **Activities (2019)**

The number of registered students: 116 (3rd and 4th grade: 73, 5th and 6th: 43)

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: 2 lectures  
Medical Research Communications: 66 lectures

Presentation of research progress: 3 times (including the retreat of MD scientist training program in the University of Tokyo)

The number of students receiving travel supports for research : 8

The number of students receiving Osamu Otsubo Tetsumon Fellowship : 14

The number of Year 6 students who passed their honors thesis defense: 2 (the Dean's Prize and the Satoshi Arima memorial fellowship were awarded to one student each)

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# Museum of Health and Medicine

## Director

Kazuhiko Ohe

## Associate

Atsushi Kitade

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

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## History and overview

The origins of the School of Medicine and the University of Tokyo Hospital can be traced back to the establishment of the Kanda Otamaga-Ike Vaccination Center in 1858. In 2008, it celebrated its 150th anniversary. The Museum of Health and Medicine was planned as part of commemorative projects to celebrate the 150th anniversary of the founding of the School and the Hospital, and was opened on January 20, 2011. One of the themes for the commemorative projects marking the 150th anniversary was the “development of communication between health science and care and society,” and the Museum of Health and Medicine forms one of the pillars of this.

In establishing the Museum of Health and Medicine, we renovated the School of Medicine’s Central Building (Medical Library), which had originally been instituted as part of the commemorative projects celebrating the 100th anniversary of the founding of the School and the Hospital. The Museum has about 400m<sup>2</sup> areas, including about 70m<sup>2</sup> of a permanent gallery and 230m<sup>2</sup> 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.

## **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.

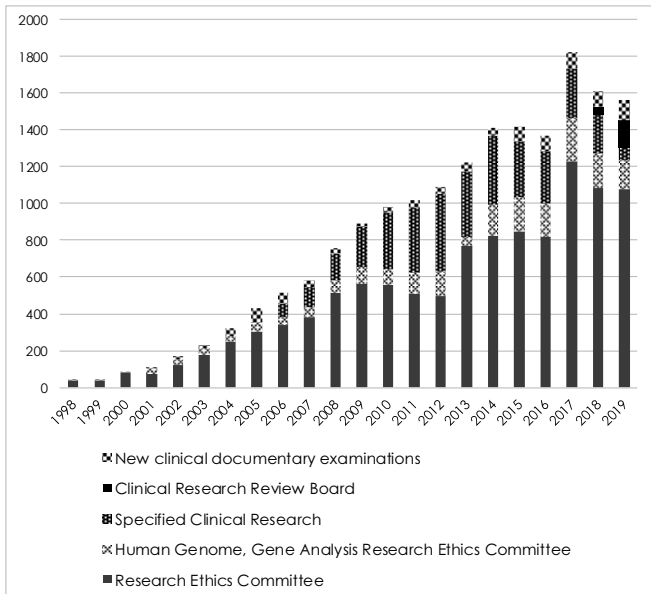
## Activities

- 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 2019

- Research Ethics Committee (except for clinical trial, GCP):  
361 new applications, 908 minor alterations of approved studies
- Clinical Research Review Board:153
- New clinical documentary examinations: 106



## 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 2019 with 2289 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.

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# 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>

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## 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 4<sup>th</sup> grade students and “tutorial PBL” for 2<sup>th</sup> 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.