ISSN 1883-9606

# 東京医学

# THE TOKYO JOURNAL OF MEDICAL SCIENCES

October 2017 Vol.135

**ANNUAL REPORT OF**

**THE GRADUATE SCHOOL OF MEDICINE**

**AND**

**THE FACULTY OF MEDICINE**

**THE UNIVERSITY OF TOKYO**

**REPORTS FOR THE PERIOD April 2016 — March 2017**

共同編集 東京医学会・東京大学医師会・東京大学医学部

JOINTLY EDITED BY

THE TOKYO SOCIETY OF MEDICAL SCIENCES

THE UNIVERSITY OF TOKYO MEDICAL SOCIETY

THE UNIVERSITY OF TOKYO FACULTY OF MEDICINE

学術刊行物

東京医学
Tokyo J. Med. Sci.

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

## REPORTS FOR THE PERIOD April 2016-March 2017

# Introduction

This is volume 135(the edition of year 2017) 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, the International Research Center for Medical Education, 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 150 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.

Kohei Miyazono, Dean
Graduate School of Medicine and Faculty of Medicine
The University of Tokyo

October, 2017

# CONTENTS

University Hospital

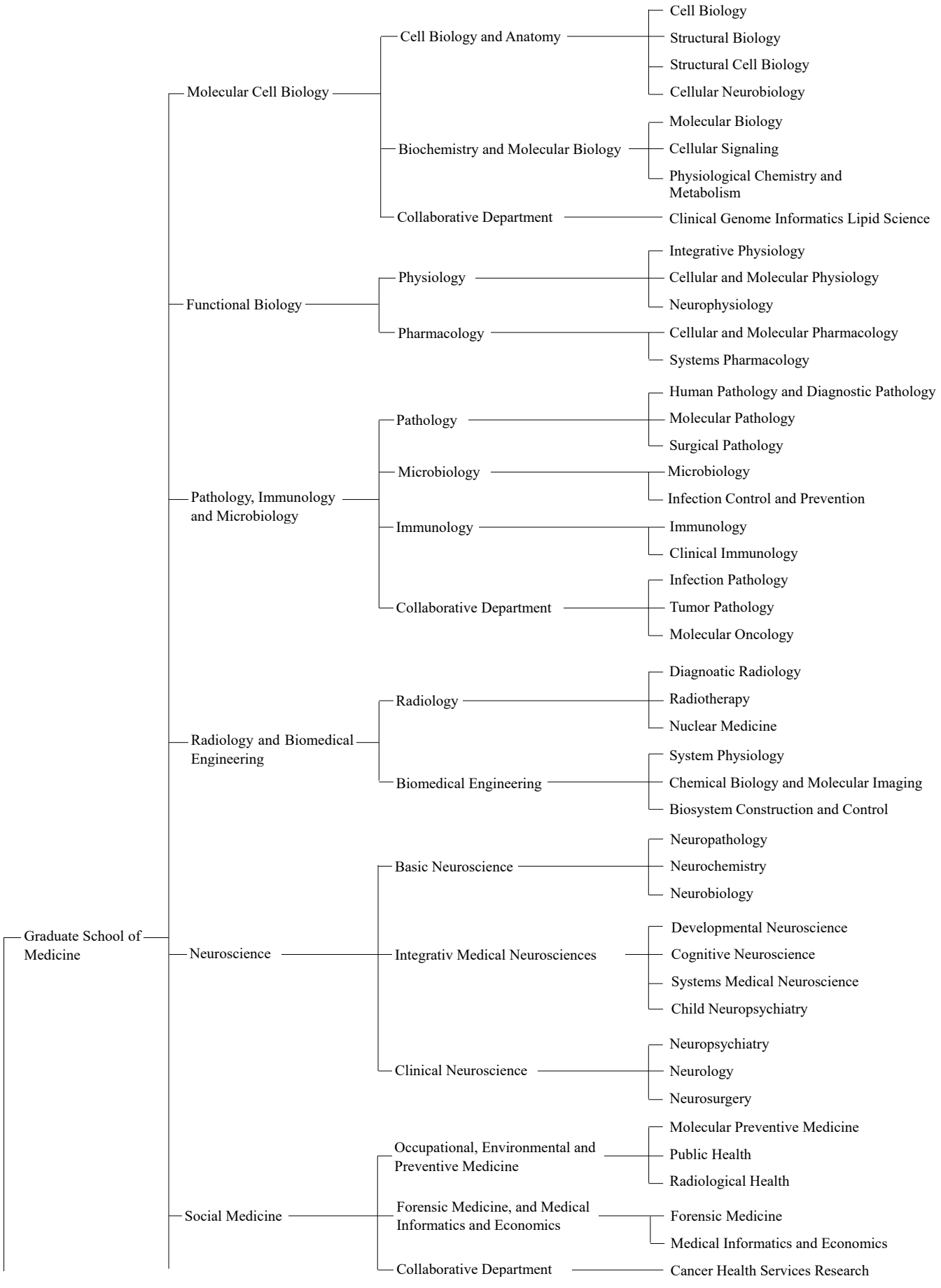
# History

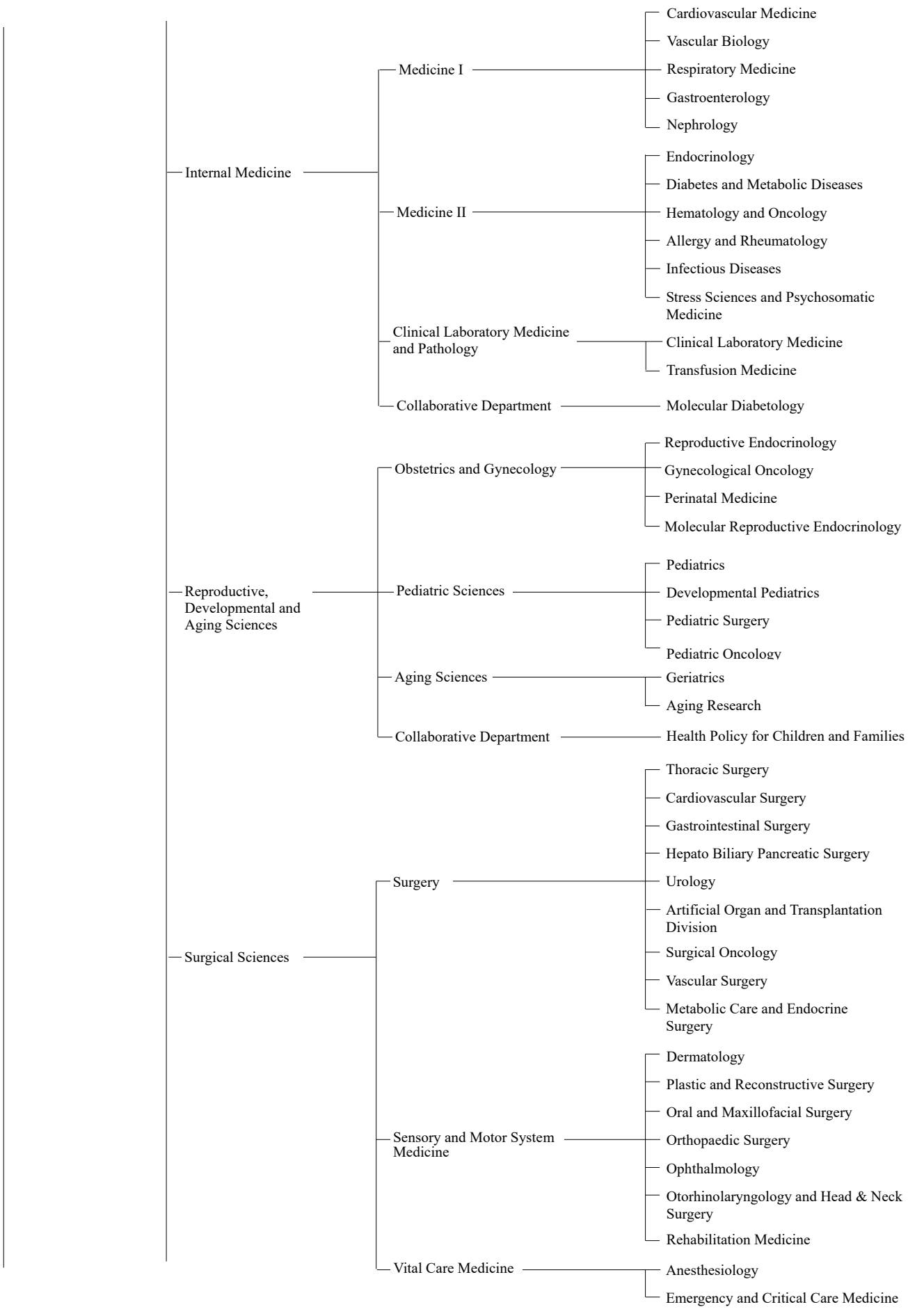
| | | |
|---|---|---|
| 1858 | May | Practitioners, trained in Dutch (European) medicine in Edo (Tokyo), laid out money to establish the Shutojo (vaccination center) in Kanda Mitamagaike. |
| | Nov. | Shutojo was destroyed in a fire that had spread from Kanda Aioicho. Shutojo continued its operations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

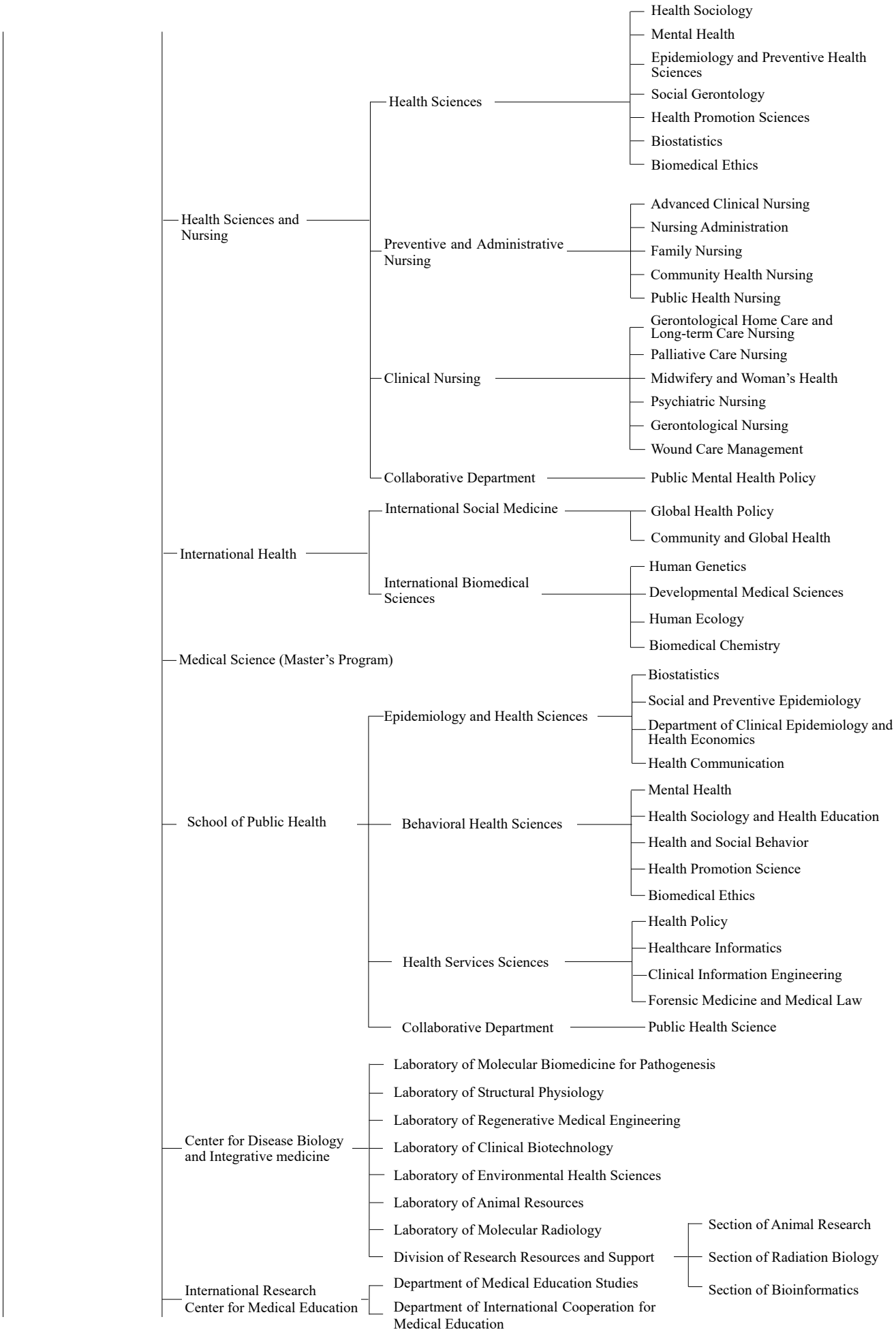
| | | |
|---|---|---|
| | Jul. | The Graduate School was founded, and the Division of Medical Doctor Biological Science was established. The Brain Research Laboratory became the Brain Research Institute of the Faculty of Medicine. |
| 1956 | Apr. | The Midwives School was established. |
| 1958 | Apr.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

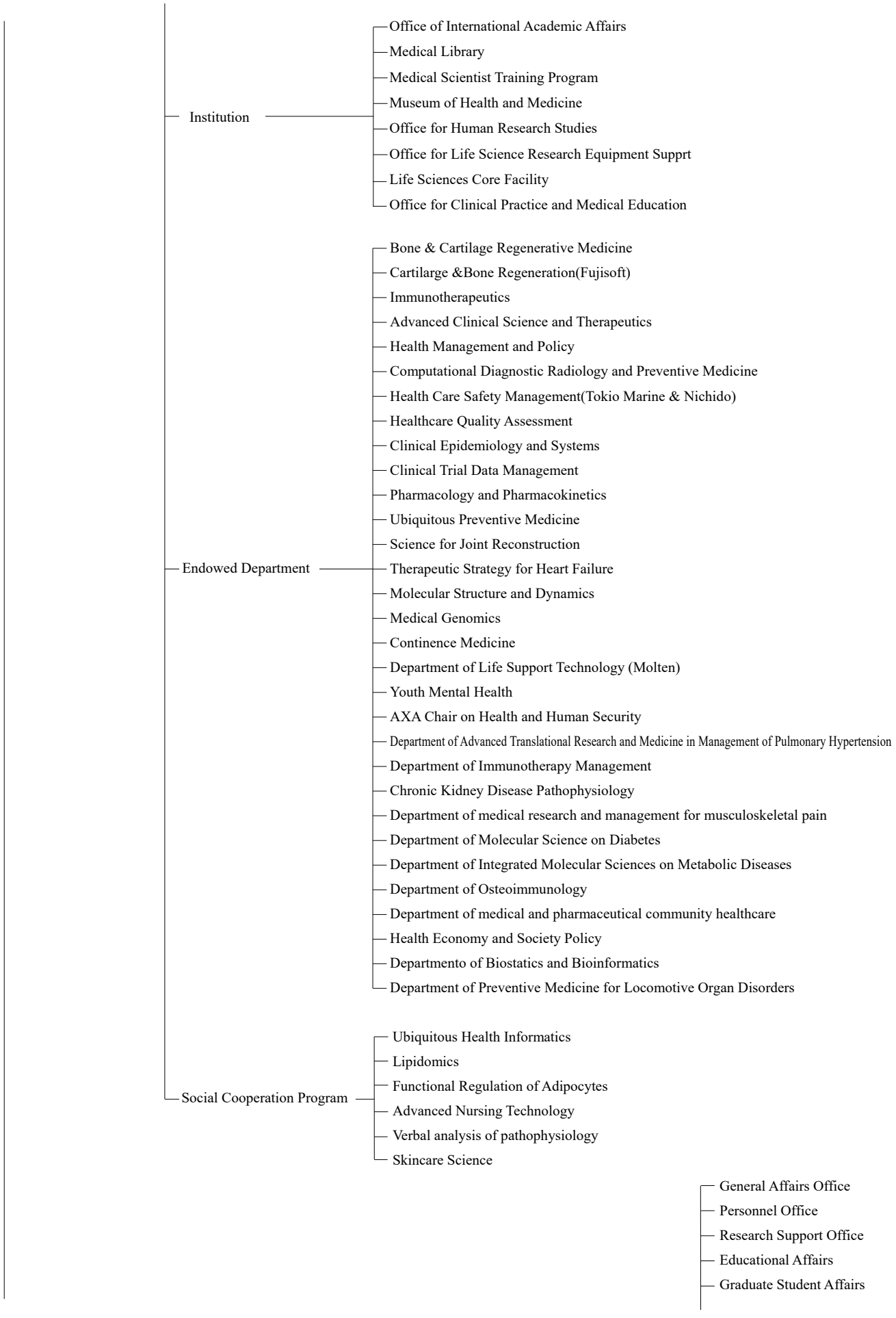
| | | |
|---|---|---|
| 2000 | Apr. | The International Research Center for Medical Education was established (A shared facility for education and research). |
| 2001 | Apr. | The University Branch Hospital was united with the University Hospital. |
| 2002 | Mar. | Nursing School and Midwives School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

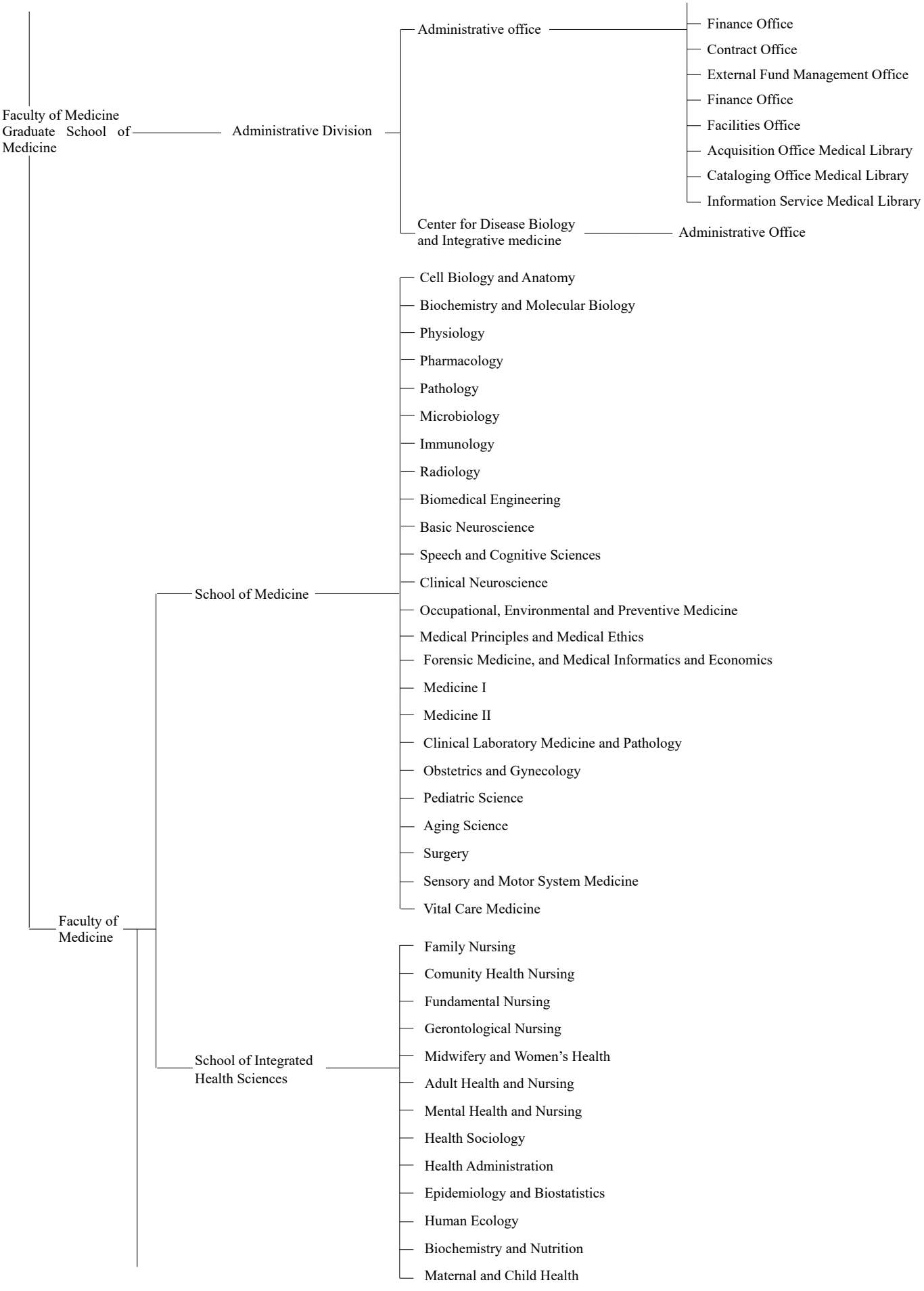
# Organization Chart

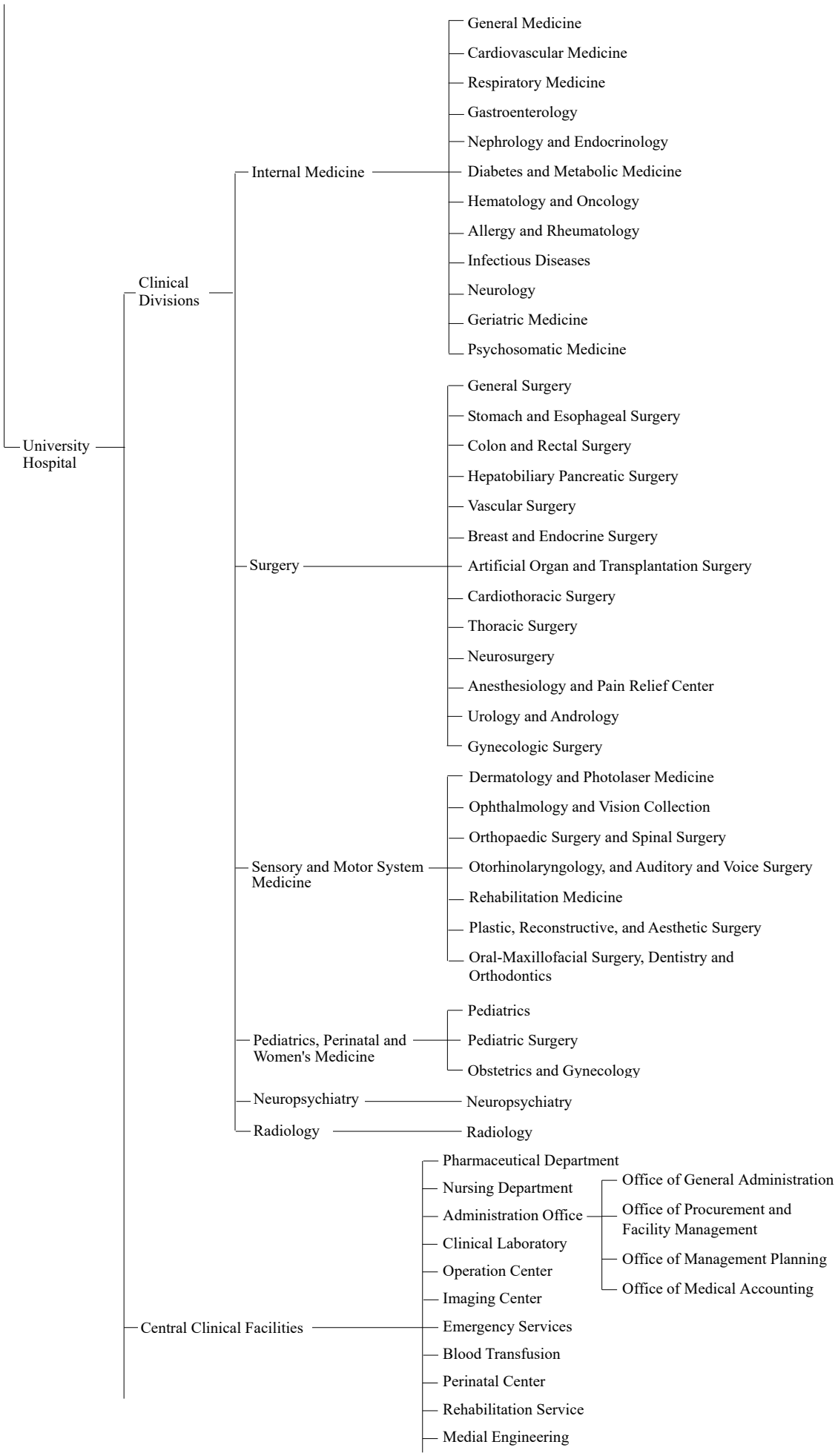


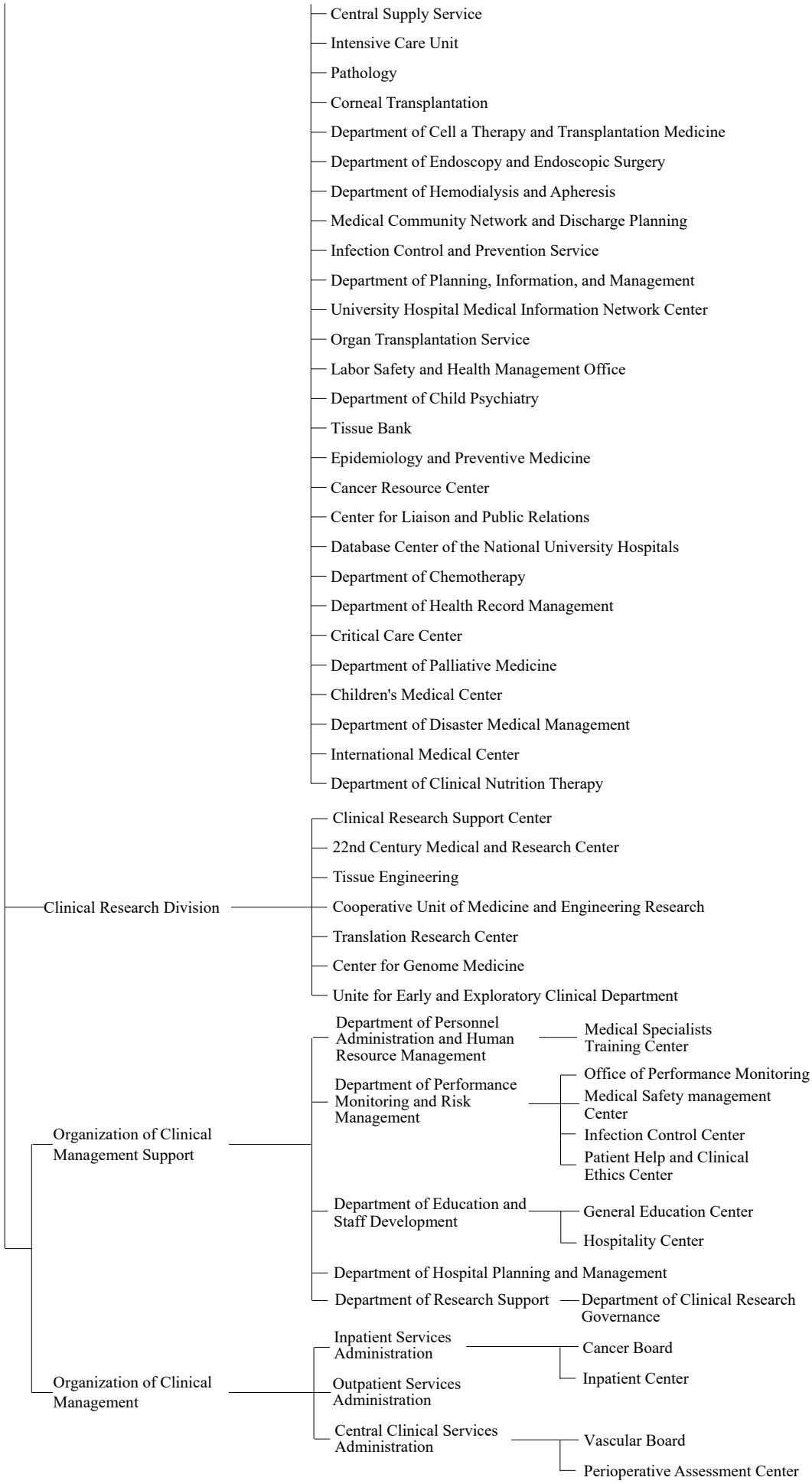

Internal Medicine
Medicine I
Cardiovascular Medicine
Vascular Biology
Respiratory Medicine
Gastroenterology
Nephrology
Medicine II
Endocrinology
Diabetes and Metabolic Diseases
Hematology and Oncology
Allergy and Rheumatology
Infectious Diseases
Stress Sciences and Psychosomatic Medicine
Clinical Laboratory Medicine and Pathology
Clinical Laboratory Medicine
Transfusion Medicine
Collaborative Department
Molecular Diabetology
Reproductive, Developmental and Aging Sciences
Obstetrics and Gynecology
Reproductive Endocrinology
Gynecological Oncology
Perinatal Medicine
Molecular Reproductive Endocrinology
Pediatric Sciences
Pediatrics
Developmental Pediatrics
Pediatric Surgery
Pediatric Oncology
Aging Sciences
Geriatrics
Aging Research
Collaborative Department
Health Policy for Children and Families
Surgical Sciences
Surgery
Thoracic Surgery
Cardiovascular Surgery
Gastrointestinal Surgery
Hepato Biliary Pancreatic Surgery
Urology
Artificial Organ and Transplantation Division
Surgical Oncology
Vascular Surgery
Metabolic Care and Endocrine Surgery
Sensory and Motor System Medicine
Dermatology
Plastic and Reconstructive Surgery
Oral and Maxillofacial Surgery
Orthopaedic Surgery
Ophthalmology
Otorhinolaryngology and Head & Neck Surgery
Rehabilitation Medicine
Vital Care Medicine
Anesthesiology
Emergency and Critical Care Medicine


Health Sciences and Nursing
Health Sciences
Health Sociology
Mental Health
Epidemiology and Preventive Health Sciences
Social Gerontology
Health Promotion Sciences
Biostatistics
Biomedical Ethics
Preventive and Administrative Nursing
Advanced Clinical Nursing
Nursing Administration
Family Nursing
Community Health Nursing
Public Health Nursing
Clinical Nursing
Gerontological Home Care and Long-term Care Nursing
Palliative Care Nursing
Midwifery and Woman's Health
Psychiatric Nursing
Gerontological Nursing
Wound Care Management
Collaborative Department
Public Mental Health Policy
International Health
International Social Medicine
Global Health Policy
Community and Global Health
International Biomedical Sciences
Human Genetics
Developmental Medical Sciences
Human Ecology
Biomedical Chemistry
Medical Science (Master's Program)
School of Public Health
Epidemiology and Health Sciences
Biostatistics
Social and Preventive Epidemiology
Department of Clinical Epidemiology and Health Economics
Health Communication
Behavioral Health Sciences
Mental Health
Health Sociology and Health Education
Health and Social Behavior
Health Promotion Science
Biomedical Ethics
Health Services Sciences
Health Policy
Healthcare Informatics
Clinical Information Engineering
Forensic Medicine and Medical Law
Collaborative Department
Public Health Science
Center for Disease Biology and Integrative medicine
Laboratory of Molecular Biomedicine for Pathogenesis
Laboratory of Structural Physiology
Laboratory of Regenerative Medical Engineering
Laboratory of Clinical Biotechnology
Laboratory of Environmental Health Sciences
Laboratory of Animal Resources
Laboratory of Molecular Radiology
Division of Research Resources and Support
Section of Animal Research
Section of Radiation Biology
Section of Bioinformatics
International Research Center for Medical Education
Department of Medical Education Studies
Department of International Cooperation for Medical Education


Institution
Office of International Academic Affairs
Medical Library
Medical Scientist Training Program
Museum of Health and Medicine
Office for Human Research Studies
Office for Life Science Research Equipment Supprt
Life Sciences Core Facility
Office for Clinical Practice and Medical Education
Endowed Department
Bone & Cartilage Regenerative Medicine
Cartilarge &Bone Regeneration(Fujisoft)
Immunotherapeutics
Advanced Clinical Science and Therapeutics
Health Management and Policy
Computational Diagnostic Radiology and Preventive Medicine
Health Care Safety Management(Tokio Marine & Nichido)
Healthcare Quality Assessment
Clinical Epidemiology and Systems
Clinical Trial Data Management
Pharmacology and Pharmacokinetics
Ubiquitous Preventive Medicine
Science for Joint Reconstruction
Therapeutic Strategy for Heart Failure
Molecular Structure and Dynamics
Medical Genomics
Continence Medicine
Department of Life Support Technology (Molten)
Youth Mental Health
AXA Chair on Health and Human Security
Department of Advanced Translational Research and Medicine in Management of Pulmonary Hypertension
Department of Immunotherapy Management
Chronic Kidney Disease Pathophysiology
Department of medical research and management for musculoskeletal pain
Department of Molecular Science on Diabetes
Department of Integrated Molecular Sciences on Metabolic Diseases
Department of Osteoimmunology
Department of medical and pharmaceutical community healthcare
Health Economy and Society Policy
Departmento of Biostatics and Bioinformatics
Department of Preventive Medicine for Locomotive Organ Disorders
Social Cooperation Program
Ubiquitous Health Informatics
Lipidomics
Functional Regulation of Adipocytes
Advanced Nursing Technology
Verbal analysis of pathophysiology
Skincare Science
General Affairs Office
Personnel Office
Research Support Office
Educational Affairs
Graduate Student Affairs


Faculty of Medicine Graduate School of Medicine
Administrative Division
Administrative office
Finance Office
Contract Office
External Fund Management Office
Finance Office
Facilities Office
Acquisition Office Medical Library
Cataloging Office Medical Library
Information Service Medical Library
Center for Disease Biology and Integrative medicine
Administrative Office
Faculty of Medicine
School of Medicine
Cell Biology and Anatomy
Biochemistry and Molecular Biology
Physiology
Pharmacology
Pathology
Microbiology
Immunology
Radiology
Biomedical Engineering
Basic Neuroscience
Speech and Cognitive Sciences
Clinical Neuroscience
Occupational, Environmental and Preventive Medicine
Medical Principles and Medical Ethics
Forensic Medicine, and Medical Informatics and Economics
Medicine I
Medicine II
Clinical Laboratory Medicine and Pathology
Obstetrics and Gynecology
Pediatric Science
Aging Science
Surgery
Sensory and Motor System Medicine
Vital Care Medicine
School of Integrated Health Sciences
Family Nursing
Comunity Health Nursing
Fundamental Nursing
Gerontological Nursing
Midwifery and Women's Health
Adult Health and Nursing
Mental Health and Nursing
Health Sociology
Health Administration
Epidemiology and Biostatistics
Human Ecology
Biochemistry and Nutrition
Maternal and Child Health


University Hospital
Clinical Divisions
Internal Medicine
General Medicine
Cardiovascular Medicine
Respiratory Medicine
Gastroenterology
Nephrology and Endocrinology
Diabetes and Metabolic Medicine
Hematology and Oncology
Allergy and Rheumatology
Infectious Diseases
Neurology
Geriatric Medicine
Psychosomatic Medicine
Surgery
General Surgery
Stomach and Esophageal Surgery
Colon and Rectal Surgery
Hepatobiliary Pancreatic Surgery
Vascular Surgery
Breast and Endocrine Surgery
Artificial Organ and Transplantation Surgery
Cardiothoracic Surgery
Thoracic Surgery
Neurosurgery
Anesthesiology and Pain Relief Center
Urology and Andrology
Gynecologic Surgery
Sensory and Motor System Medicine
Dermatology and Photolaser Medicine
Ophthalmology and Vision Collection
Orthopaedic Surgery and Spinal Surgery
Otorhinolaryngology, and Auditory and Voice Surgery
Rehabilitation Medicine
Plastic, Reconstructive, and Aesthetic Surgery
Oral-Maxillofacial Surgery, Dentistry and Orthodontics
Pediatrics, Perinatal and Women's Medicine
Pediatrics
Pediatric Surgery
Obstetrics and Gynecology
Neuropsychiatry
Neuropsychiatry
Radiology
Radiology
Central Clinical Facilities
Pharmaceutical Department
Nursing Department
Administration Office
Office of General Administration
Office of Procurement and Facility Management
Office of Management Planning
Office of Medical Accounting
Clinical Laboratory
Operation Center
Imaging Center
Emergency Services
Blood Transfusion
Perinatal Center
Rehabilitation Service
Medial Engineering


Central Supply Service
Intensive Care Unit
Pathology
Corneal Transplantation
Department of Cell a Therapy and Transplantation Medicine
Department of Endoscopy and Endoscopic Surgery
Department of Hemodialysis and Apheresis
Medical Community Network and Discharge Planning
Infection Control and Prevention Service
Department of Planning, Information, and Management
University Hospital Medical Information Network Center
Organ Transplantation Service
Labor Safety and Health Management Office
Department of Child Psychiatry
Tissue Bank
Epidemiology and Preventive Medicine
Cancer Resource Center
Center for Liaison and Public Relations
Database Center of the National University Hospitals
Department of Chemotherapy
Department of Health Record Management
Critical Care Center
Department of Palliative Medicine
Children's Medical Center
Department of Disaster Medical Management
International Medical Center
Department of Clinical Nutrition Therapy
Clinical Research Division
Clinical Research Support Center
22nd Century Medical and Research Center
Tissue Engineering
Cooperative Unit of Medicine and Engineering Research
Translation Research Center
Center for Genome Medicine
Unite for Early and Exploratory Clinical Department
Organization of Clinical Management Support
Department of Personnel Administration and Human Resource Management
Medical Specialists Training Center
Department of Performance Monitoring and Risk Management
Office of Performance Monitoring
Medical Safety management Center
Infection Control Center
Patient Help and Clinical Ethics Center
Department of Education and Staff Development
General Education Center
Hospitality Center
Department of Hospital Planning and Management
Department of Research Support
Department of Clinical Research Governance
Organization of Clinical Management
Inpatient Services Administration
Cancer Board
Inpatient Center
Outpatient Services Administration
Central Clinical Services Administration
Vascular Board
Perioperative Assessment Center

# Teaching, Research, Secretarial and Administrative Staffs

## Chief Members of Administration

| | |
|---|---|
| Dean, Graduate School of Medicine | Kohei Miyazono |
| (Dean, Faculty of Medicine) | |
| Chairman, School of Health Sciences and Nursing | Hiromi Sanada |
| Director, Medical Library | Tsuyoshi Takato |
| Director General, University Hospital | Nobuhito Saito |
| Director, Center for Disease Biology and Integrative Medicine | Shigeo Okabe |
| Director, International Research Center for Medical Education | Kazuhiko Yamamoto |

## Graduate School of Medicine

**Molecular Cell Biology**

| | | |
|---|---|---|
| Department of Cell Biology and Anatomy | Professor | Masahide Kikkawa |
| | Professor | Shigeo Okabe |
| Department of Biochemistry and Molecular Biology | Professor | Noboru Mizushima |
| | Professor | Hiroyuki Mano |
| | Professor | Hiroki Kurihara |

**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 | Masashi Fukayama |
| | 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 | Yasuteru Urano |

**Neuroscience**

| | | |
|---|---|---|
| Department of Basic Neuroscience | Professor | Takeshi Iwatsubo |
| | Professor | Haruhiko Bito |
| | Professor | Kenzo Hirose |

| | | |
|---|---|---|
| Department of Integrative Medical Neuroscience | | |
| Department of Clinical Neuroscience | Professor | Kiyoto Kasai |
| | Professor | Shoji Tsuji |
| | Professor | Nobuhito Saito |
| **Social Medicine** | | |
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| | Professor | Yasuki Kobayashi |
| Department of Forensic Medicine, and Medical Informatics and Economics | Professor | Hirotaro Iwase |
| | Professor | Kazuhiko Ohe |
| **Internal Medicine** | | |
| Department of Medicine I | Professor | Issei Komuro |
| | Professor | Takahide Nagase |
| | Professor | Kazuhiko koike |
| Department of Medicine II | Professor | Masaomi Nangaku |
| | Professor | Takashi Kadowaki |
| | Professor | Mineo Kurokawa |
| | Professor | Kazuhiko Yamamoto |
| | Professor | Kyoji Moriya |
| Department of Clinical Laboratory Medicine and Pathology | Professor | Yutaka Yatomi |
| | Professor | Hitoshi Okazaki |
| **Reproductive, Developmental and Aging Science** | | |
| Department of Obstetrics and Gynecology | Professor | Tomoyuki Fujii |
| | Professor | Yutaka Osuga |
| Department of Pediatric Science | Professor | Akira Oka |
| Department of Aging Science | Professor | Masahiro Akishita |
| **Surgical Sciences** | | |
| Department of Surgery | Professor | Jun Nakajima |
| | Professor | Minoru Ono |
| | Professor | Yasuyuki Seto |
| | Professor | Norihiro Kokudo |
| | Professor | Yukio Homma |
| | Professor | Toshiaki Watanabe |
| Department of Sensory and Motor System Medicine | Professor | Shinichi Sato |
| | Professor | Isao Koshima |
| | Professor | Tsuyoshi Takato |
| | Professor | Sakae Tanaka |
| | Professor | Makoto Aihara |
| | Professor | Tatsuya Yamasoba |
| | Professor | Nobuhiko Haga |

| | | |
|---|---|---|
| Department of Vital Care Medicine | Professor | Yoshitsugu Yamada |
| | Professor | Naoto Morimura |
| **Health Sciences and Nursing** | | |
| Department of Health Sciences | Professor | Norito Kawakami |
| | Professor | Yutaka Matsuyama |
| | Professor | Hideki Hashimoto |
| | Professor | Akira Akabayashi |
| Department of Preventive and Administrative Nursing | Professor | Kiyoko Kamibeppu |
| Department of Clinical Nursing | Professor | Noriko Yamamoto |
| | Professor | Norito Kawakami |
| | Professor | Hiromi Sanada |
| **International Health** | | |
| Department of International Social Medicine | Professor | Kenji Shibuya |
| | Professor | Masamine Jinba |
| Department of International Biomedical Sciences | Professor | Katsushi Tokunaga |
| | Professor | Masashi Mizuguchi |
| | Professor | Chiho Watanabe |
| | Professor | Tomoyoshi Nozaki |
| **School of Public Health** | | |
| Department of Epidemiology and Health Sciences | Professor | Yutaka Matsuyama |
| | Professor | Satoshi Sasaki |
| | Professor | Hideo Yasunaga |
| | Professor | Takahiro Kiuchi |
| Department of Behavioral Health Sciences | Professor | Norito Kawakami |
| | Professor | Hideki Hashimoto |
| | Professor | Akira Akabayashi |
| Department of Health Services Sciences | Professor | Yasuki Kobayashi |
| | Professor | Kazuhiko Ohe |
| | Professor | Hiroshi Oyama |
| | Professor | Hirotaro Iwase |

| | | |
|---|---|---|
| **Center for Disease Biology and Integrative Medicine** | | |
| Laboratory of Molecular Biomedicine for pathogenesis | Professor | Toru Miyazaki |
| Laboratory of Structural Physiology | Professor | Haruo Kasai |
| Laboratory of Regenerative Medical Engineering | Professor | Takashi Azuma |
| Laboratory of Clinical Biotechnology | Professor | Ungil Chung |
| 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 | Kazuhiko Yamamoto |
| **Medical Library** | Professor | Tsuyoshi Takato |
| **International Academic Affairs** | Professor | Yasuyuki Seto |
| **Medical Scientist Training Program** | Professor | Haruhiko Bito |
| **Museum of Health and Medicine** | Professor | Kazuhiko Ohe |
| **Office for Human Research Studies** | Professor | Yutaka Yatomi |
| **Life Sciences Core Facility** | Associate Professor | Yoshihiro Kita |
| **Office for Clinical Practice and Medical Education** | Professor | Tatsuya Yamasoba |
| **Endowed Departments** | | |
| Department of Bone & Cartilage Regenerative Medicine | Project Associate professor | Takumi Matsumoto |
| Department of Cartilage & Bone Regeneration(Fujisoft) | Project Associate professor | Atsuhiko Hikita |
| Immunotherapeutics | Project Professor | Kazuhiro Kakimi |
| Department of Advanced Clinical Science and Therapeutics | Project Associate professor | Junichi Suzuki |
| Computational Diagnostic Radiology and Preventive Medicine | Project Professor | Naoto Hayashi |
| | Project Associate professor | Kansei Uno |
| | Project Associate professor | Takeharu Yoshikawa |
| Healthcare Safety Management (Tokio Marine & Nichido) | Project Associate professor | Masaki Anraku |
| The Department of Healthcare Quality Assessment | Project Professor | Hiroaki Miyata |
| | Project Associate professor | Shun Kohsaka |
| Pharmacology and Pharmacokinetics | Project Associate professor | Masashi Honma |
| 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 Medical Genomics | Project Associate professor | Eirin Sai |
| Continence medicine | Project Professor | Yasuhiko Igawa |
| Department of Life Support Technology (Molten) | Project Associate professor | Taketoshi Mori |
| Department of Youth Mental Health | Project Associate professor | Tsuyoshi Araki |

| | | |
|---|---|---|
| Department of Advanced Nephrology and Regenerative Medicine | Project Associate professor | Keiichi Hishikawa |
| AXA Chair on Health and Human Security | Project Professor | Manami Inoue |
| Department of Advanced Translational Research and Medicine in Management of Pulmonary Hypertension | Project Associate professor | Hideki Takimoto |
| Department of Immunotherapy Management | Project Associate professor | Hiroko Kanda |
| Chronic kidney disease pathophysiology | Project Associate professor | Reiko Inagi |
| Department of medical research and management for musculoskeletal pain | Project Professor | Koh Matsudaira |
| | Project Associate professor | Hiroyuki Oka |
| Department of Molecular Science on Diabetes | Project Associate professor | Hironori Waki |
| Department of Integrated Molecular Sciences on Metabolic Diseases | Project Associate professor | Masato Iwabu |
| Department of Osteoimmunology | Project Associate professor | Kazuo Okamoto |
| Department of medical and pharmaceutical community healthcare | Project Associate 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 |

**Social Cooperation Program**

| | | |
|---|---|---|
| Department of Ubiquitous Health Informatics | Project Associate professor | Kayo Waki |
| Department of Lipidomics | Project Professor | Takao Shimizu |
| | Project Associate professor | Fuyuki Tokumasu |
| Advanced Nursing Technology | Project Associate professor | Ryoko Murayama |
| Verbal analysis of pathophysiology | Project Associate professor | Shinichi Tokuno |
| Department of Health Services Research | Project Associate professor | Taisuke Jo |
| Skincare Science | Project Associate professor | Takeo Minematsu |

**University Hospital**

**Clinical Divisions**

| | | |
|---|---|---|
| General Medicine | Head | Mineo Kurokawa |
| 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 | Takashi Kadowaki |
| Hematology and Oncology | Head | Mineo Kurokawa |
| Allergy and Rheumatology | Head | Kazuhiko Yamamoto |

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|---|---|---|
| Infectious Diseases | Head | Kyoji Moriya |
| Neurology | Head | Shoji Tsuji |
| Geriatric Medicine | Head | Masahiro Akishita |
| Psychosomatic Medicine | Head | Kazuhiro Yoshiuchi |
| General Surgery | Head | Norihiro Kokudo |
| Stomach and Esophagus Surgery | Head | Yasuyuki Seto |
| Colon and Rectal Surgery | Head | Toshiaki Watanabe |
| Hepatobiliary Pancreatic Surgery | Head | Norihiro Kokudo |
| Vascular Surgery | Head | Toshiaki Watanabe |
| Breast and Endocrine Surgery | Head | Keiichiro Tada |
| Artificial organ and Transplantation Surgery | Head | Norihiro Kokudo |
| Cardiovascular Surgery | Head | Minoru Ono |
| Thoracic Surgery | Head | Jun Nakajima |
| Neurosurgery | Head | Nobuhito Saito |
| Anesthesiology and Pain Relief Center | Head | Yoshitsugu Yamada |
| Urology and Andrology | Head | Yukio Honma |
| Gynecologic Surgery | Head | Yutaka Ohsuga |
| Dermatology and Photolaser Medicine | Head | Shinichi Sato |
| Ophthalmology and Vision Collection | Head | Makoto Aihara |
| Orthopaedic Surgery and Spinal Surgery | Head | Sakae Tanaka |
| Otorhinolaryngology and Auditory and Voice Surgery | Head | Tatsuya Yamasoba |
| Rehabilitation Medicine | Head | Nobuhiko Haga |
| Plastic, Reconstructive and Aesthetic Surgery | Head | Isao Koshima |
| Oral-Maxillofacial Surgery Dentistry and Orthodontics | Head | Tsuyoshi Takato |
| Pediatrics | Head | Akira Oka |
| Pediatric Surgery | Head | Jun Fujishiro |
| Obstetrics and Gynecology | Head | Tomoyuki Fujii |
| Neuropsychiatry | Head | Kiyoto Kasai |
| Radiology | Head | Osamu Abe |
| **Central Clinical Facilites** | | |
| Pharmaceutical Department | Head | Hiroshi Suzuki |
| Department of Clinical Laboratory | Head | Yutaka Yatomi |
| Surgical Center | Head | Hiroshi Yasuhara |
| Imaging Center | Head | Osamu Abe |
| Emergency Service | Head | Naoto Morimura |
| Department of Blood Transfusion | Head | Hitoshi Okazaki |
| Perinatal Center | Head | Tomoyuki Fujii |
| Rehabilitation Center | Head | Nobuhiko Haga |
| Department of Medical Engineering | Head | Kyouhiro Chou |

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|---|---|---|
| Central Supply Service | Head | Kazuhiko Fukatsu |
| Intensive Care Unit | Head | Naoto Morimura |
| Pathology | Head | Masashi Fukayama |
| Department of Corneal Transplantation | Head | Tomohiko Usui |
| Department of Cell Therapy and Transplantation Medicine | Head | Mineo Kurokawa |
| Department of Endoscopy and Endoscopic Surgery | Head | Mitsuhiro Fujisiro |
| Department of Hemodialysis and Apheresis | Head | Masaomi Nangaku |
| Medical Community Network and Discharge Planning | Head | Kiyoto Kasai |
| Infection Control and Prevention Service | Head | Kyoji Moriya |
| Department of Planning, Information and Management | Head | Kazuhiko Ohe |
| University Hospital Medical Information Network Center | Head | Hirono Ishikawa |
| Organ Transplantation Service | Head | Norihiro Kokudo |
| Labor Safety and Health Management Office | Head | Tomotaka Yamamoto |
| Child Psychiatry | Head | Yukiko Kano |
| Tissue Bank | Head | Sumihito Tamura |
| Epidemiology and Preventive Medicine | Head | Tsutomu Yamazaki |
| Cancer Resource Center | Head | Sachiyo Nomura |
| Center for Liaison and Public Relations | Head | Toshiaki Watanabe |
| Department of Chemotherapy | Head | Norihiro Kokudo |
| Department of Medical Record Management | Head | Toshiaki Watanabe |
| Critical Care Center | Head | Naoto Morimura |
| Department of 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 |
| Clinical Research Support Center | Head | Tsutomu Yamazaki |
| 22nd Century Medical and Research Center | Head | Tsuyoshi Takato |
| Department of Tissue Engineering | Head | Tsuyoshi Takato |
| Cooperative Unit of Medicine and Engineering Research | Head | Minoru Ono |
| Translational Research Center | Head | Mineo Kurokawa |
| Center for Genome Medicine | Head | Shoji Tsuji |
| 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 and Associate**

Yosuke Tanaka, M. D., Noriko Homma, Ph. D.,

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

## Teaching activities

Our teaching responsibility is following.

I.

1) Lecture on Cell Bilogy, Developmental Biology, Histology and Neurocytology.
2) Lecture on Gross Anatomy and Neuroanatomy. to medical students and students of other faculties

II.

1) Laboratory course of Gross Anatomy and Neuroanatomy.
2) Laboratory course of Histology and Histology of the Cenrtral Nervous System.

to medical students and students of other faculties.

In addition we offer a special training course (free quarter) of various kinds of molecular cell biology techniques such as immunocytochemistry, electron microscopy, biochemistry, molecular biology, 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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# Department of Cell Biology & Anatomy (Structural Biology)

**Professor**

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

**Research Associate**

Haruaki Yanagisawa, Ph. D, Tsukasa Makino, Ph. D.

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

## Introduction and Organization

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

Currently the lab members include: Masahide Kikkawa (professor), Haruaki Yanagisawa, Tsukasa Makino (research associates), Akihisa Tsutsumi (project research associate), Hiroshi Yamaguchi (project researcher), Yuma Tani, Tatsuki Abe, Genta Morikawa (MSTP students), Akiko Oosakaya, Akiko Koikeda, Ayako Ogasawara (technical assistant) and Mikako Yanagiuchi (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 is 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 macro-molecular complexes such as axonemes. We have been developing new techniques, such as asymmetric helical reconstruction and Ruby-Helix software.

Cryo-electron tomography is also used for visualizing more complex cellular structures such as eukaryotic cilia/flagella. In combination with genetics, it is now possible to identify the 3D positions of specific gene product.

**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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4. Oda T., T. Abe, H. A. Yanagisawa, and M. Kikkawa
   "Structure and function of outer dynein arm intermediate and light chain complex"
   *Molecular Biology of the Cell*, 27:1051-9, 2016

# Department of Cellular Neurobiology

**Professor**

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

**Lecturer**

Hirohide Iwasaki, Ph.D

**Research Associate**

Shinji Tanaka, Ph.D., Hiroaki Oshiro, Ph.D.

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

## Introduction and Organization

The Department of Cellular Neurobiolgy was initially established as Neuroanatomy department of former Brain Institute of Medical School of Imperial University of Tokyo in 1936. Since the structural reconstruction of School of Medicine in 1997 this department became one of the departments of Cell Biology and Anatomy of Graduate School of Medicine. This department is currently organized by Professor Shigeo Okabe since September in 2007. The department is constituted of other 30 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 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 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 a long term to realize fidelity of various animal behaviors, but also should be altered rapidly when animals adapt to a new environment. Molecular basis of this dichotomy, which is unique to synapses, is the main interest of our laboratory.

**Synapse formation during development**

Synapse is one of the major elements to transduce information from neuron to neuron. Most of the synapses are formed during the early development and thereafter they become stable after the intensive pruning. We are interested in how synapse is formed 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 some PSD proteins and examine their roles in synapse formation and maintenance.

Two-photon excitation microscopy allows imaging of living brain. We examine synapse remodeling in

vivo by observing the postsynaptic structures and some PSD proteins tagged by fluorescent proteins. We are also investigating abnormality of synapse remodeling in developmental disorders by using some mouse models. Our laboratory is investing the properties and molecular basis of synapses in vitro and in vivo by various imaging techniques.

## Publications


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   Quantification of sympathetic hyperinnervation and denervation after myocardial infarction by three-dimensional assessment of the cardiac sympathetic network in cleared transparent murine hearts
   **PLoS One** in press.
2. **Okabe, S.**
   Fluorescence imaging of synapse dynamics in normal circuit maturation and in developmental disorders.
   **Proceedings of the Japan Academy, Series B.** in press.
3. Nakai, N., Nagano M., Saitow F, Watanabe W., Kawamura Y., Kawamoto A., Tamada K., Mizuma H., Onoe H., Watanabe Y., Monai H., Hirase H., Nakatani J., Inagaki H., Kawada T., Miyazaki T., Watanabe M., Sato Y., **Okabe S.,** Kitamura K., Kano M., Hashimoto K., Suzuki H., and T. Takumi
   Serotonin Rebalances Cortical Tuning and Behavior Linked to Autism Symptoms in 15q11-13 CNV Mice
   **Science Advances** 3, e1603001, 2017, doi; 10.1126/sciadv.1603001
4. Hirai, S., Hotta, K., Kubo, Y., Nishino, A, **Okabe, S.**, Okamura, Y. and H.Okado
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   Temporal Changes in the response of SVZ neural stem cells to intraventricular administration of growth factors.
   **Brain Research** 1636, 119-129, 2016. doi: 10. 1016/j.brainres.2016.01.046.
8. Hayashi, A., Asanuma, D., Kamiya, M., Urano, U. and **S. Okabe**.
   High affinity receptor labeling based on basic leucine zipper domain peptides conjugated with pH-sensitive fluorescent dye: visualization of AMPA type glutamate receptor endocytosis in living neurons.
   **Neuropharmacology** 100, 66-75, 2016. doi: 10. 1016/j.neuropharm.2015.07.026.

# Molecular Cell Biology

## 2. Biochemistry and Molecular Biology

# Department of Molecular Biology

**Professor**

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

**Lecturer**

Hayashi Yamamoto, Ph.D.

**Research Associate**

Akiko Kuma, Ph.D., Hideaki Morishita, M.D., Ph.D.

**Homepage http://molbiol.umin.jp/**

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

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

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

Professor Norio Shimazono, a graduate of the Imperial University of Tokyo Faculty of Medicine in 1928, became a professor at Niigata Medical School. In 1952 he succeeded Professor Kodama. He studied vitamin B1/ cocarboxylase, ketoacid metabolism and hexose metabolism.

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

Professor Masami Muramatsu graduated from the University of Tokyo Faculty of Medicine in 1955. He

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

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

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

## Research Activities

Our current study focuses on the understanding of the molecular mechanism and physiological roles of autophagy.

1. **Molecular mechanism of autophagy**

   Autophagy is one of the major degradation pathways in the cell (1). In autophagy, intracellular components are sequestered by autophagosomes and then degraded upon fusion with lysosomes. Yeast genetic studies have identified more than 30 autophagy-related (*ATG*) genes (2). 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) fusion between the autophagosome and lysosome, and (5) recognition of selective substrates.

   In 2016, we reported the following novel findings. Autophagy-related (ATG) conjugation systems are thought to be important for a late step of autophagosome formation, their precise function has been poorly understood because they are also required for localization of the most important autophagosomal marker LC3. In our recent study, we found that, using the autophagosomal SNARE syntaxin 17 as an alternative marker, autophagosome-like structures were generated in ATG conjugation system-deficient cells. Those structures could fuse with lysosomes but the degradation of the inner autophagosomal membrane was significantly delayed. We suggest that the ATG conjugation-dependent closure of autophagosomes causes the inner autophagosomal membrane sensitive to lysosomal degradation.

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 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. Damaged mitochondria can also be eliminated by autophagy (called "mitophagy") and this function is linked to pathogenesis of Parkinson disease.

   In 2016, we reported a novel mouse model. Although Atg5-null mice are neonatal lethal, we found that these mice can be rescued by neuron-specific transgenic expression of ATG5,

suggesting that the primary cause of lethality is neuronal dysfunction including suckling failure. The rescued *Atg5*-null mouse model, as a novel resource, allows us to investigate the physiological roles of autophagy in the whole body after the neonatal period. These rescued mice demonstrate previously unappreciated abnormalities such as hypogonadism and iron-deficiency anemia. These observations provide new insights into the physiological roles of the autophagy factor ATG5.

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 probe, GFP-LC3-RFP-LC3ΔG, to assess autophagic flux. Upon intracellular expression, the probe is cleaved by ATG4 family proteases into equimolar amounts of GFP-LC3 and RFP-LC3ΔG. The former is degraded by autophagy while the latter persists as an internal control in the cytosol. Autophagic flux can thus be quantified by obtaining the ratio of GFP:RFP signals. Using this method, we have identified several autophagy-modulating drugs by screening an approved drug library. We have also demonstrated that induced and basal autophagic flux can be monitored in zebrafish and mice.

## 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 course students, the molecular biology course consisting of lectures and experiments is provided.

## Publication


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6. Noda, N.N., Mizushima, N. Atg101: not just an accessory subunit in the autophagy-initiation complex. ***Cell Struct. Funct.*** 41: 13-20 (2016).

# Department of Cellular Signaling

**Professor**

Hiroyuki Mano, M.D., Ph.D.

**Associate Professor**

Yoshihiro Yamashita, M.D., Ph.D.

**Assistant Professors**

Manabu Soda, M.D., Ph.D., Toshihide Ueno, Ph.D.

**Homepage http://mano-lab.umin.jp/english/index.html**

## Introduction and Organization

Cancer is the leading cause of adult deaths in developed countries. While the incidence of brain stroke– and heart attack–related deaths is rapidly decreasing, that of cancer-related ones is still linearly increasing today. More than eight millions of people die of cancer every year worldwide, and, even only in Japan, >30,000 of people die of cancer.

We aim to discover essential growth driver genes in cancer, and to develop reliable biomarkers and molecular targeted therapies by using original functional screening systems as well as genomics approaches.

In addition to the members shown above, two postdoctoral fellows, two research fellows, four graduates, two undergraduates, four research technicians and one secretaries belong to our department. We are also in a tight collaboration with Department of Medical Genomics.

## Teaching activities

We jointly take the responsibility for the lectures of Biochemistry as well as training of biochemical experiments. We accept students for Free Quarter and short laboratory courses. We further deliver lectures for Graduate School of Medicine, and accept graduate students.

## Research activities

Department of Cellular Signaling tries to fulfill our goals mainly through two 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.

(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 mainly use HiSeq2500 and HiSeq2000 systems for NGS, and have developed in-house computational pipelines for detecting somatic single nucleotide variations, insertions/ deletions, and chromosomal rearrangemetns.

By coupling such approaches, we have obtained following findings this year.

Sequencing mRNA of leukemic blasts in acute lymphoblastic leukemia (ALL) of adolescent and young adult (AYA) generation revealed that the novel and most frequent oncogene, *DUX4-IGH*, in B-cell ALL. Pro-B cells artificially expressing *DUX4-IGH* gave rise to B-cell ALL in mice *in vivo*. Interestingly, *DUX4-IGH* is preferentially present in the AYA generation, less frequently in childhood ALL, but never in adult ALL. Gene expression profiling of *DUX4-IGH*positive leukemic blasts revealed that it resembles that of non-Ph-like ALL, indicating that *DUX4-IGH* can become a biomarker for better prognosis.

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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 fellows, 3 visiting researchers, 11 graduate students (doctor course 7, master course 4), 1 technical staff and 2 secretaries. 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 "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. We also provide a monthly training course of theoretical biology for young researchers and students in cooperation with the members of Institute for Biology and Mathematics of Dynamical Cell Processes (iBMath), The University of Tokyo (lead by Professor Yasuo Ihara) and Core Research for Evolutional Science and Technology (CREST), Japan Science and Technology Agency.

## Research Activities

1. Developmental Biology and Medicine

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

(1) Craniofacial development

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

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

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-independet mechanisms, whereas ET-1/ETAR signaling is involved in ventral identification of the pharyngeal arches through $G_{q/11}$-mediated, Dlx5/Dlx6-dependet mechanisms. These findings indicate that the ET-1/ETAR signaling pathway is involved in craniofacial and cardiac development through different trimeric G-proteins.

(3) Angiogenesis

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

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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, Department of Molecular Biology in Graduate School of Pharmaceutical Sciences and Department of Chemical Pharmacology in Grauate School of Pharmaceutical Sciences. As part of a 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) Functional columns in the cerebral cortex are believed to be essential to process sensory information such as orientation selectivity. However, neurons in rodent visual cortex are organized in a mixed salt-and-pepper fashion for orientation selectivity. If the connections between neurons are random,

information from different orientations would be mixed, and orientation selectivity would be largely lost. Sharp orientation tuning without functional clustering suggests the existence of specific connections among similarly tuned excitatory neurons. Indeed, networks of specifically connected subpopulation of excitatory neurons — subnetworks — have been found in rodent visual cortex, and they are related to the orientation selectivity of these neurons. In our lab, we examine whether a developmental basis exists for such subnetworks.

It has been long debated to what extent neuronal functions are determined genetically or by postnatal experience or neuronal activity. However, how the function of neurons in the cortex is influenced by prenatal development is not well understood. In the embryonic stage of cortical development, progenitor cells in the ventricular zone produce excitatory neurons that migrate into the cortical plate using radial glial fibers as a scaffold. Interestingly, in the rodent cortex, clonally related sister neurons are not tightly packed. Instead, they are sparsely distributed through layers 2–6, spanning several radial minicolumns, in such a way that sister neurons derived from a given progenitor are separated from each other by neurons derived from other progenitors. We wonder whether there is any relation between the scattered progeny of single progenitors and the scattered salt-and-pepper orientation map in rodent visual cortex.

Recent studies reported that the progeny of single progenitor cells are preferentially connected to each other. These results suggest that clonally related neurons may participate in specific subnetworks in adult cortex. Since cells with similar response selectivity also have high probabilities of synaptic connection, we hypothesize that sister cells may share similar response selectivity.

We image a mouse in which all cells derived from a single cortical progenitor are labeled. By imaging all the upper layer cells of a single cortical clone, we obtain a near-complete picture of the functional properties of the cells in a cortical clone. We observe that more than half of, but not all, clonally related cells share response selectivity, indicating that cell lineage is partly responsible for the functional properties of mature neurons.

We find that the orientation preference of sister cells is not totally determined by clonal identity, as some sister cells show orientation preference different from the majority of sister cells. We hypothesize that the preferential connectivity between sister cells makes loose scaffolds that accept inputs from the thalamus and give rise to networks that share similar functional properties, such as orientation selectivity. Clonal identity cannot be the only factor determining the response selectivity of neurons, and other mechanisms, such as activity-dependent processes, may influence this scaffold and determine the final selectivity of cortical neurons in adult animals.

Our findings may explain the salt-and-pepper functional architecture in rodent visual cortex. In mice, neurons derived from the same progenitors tend to share orientation preference, and neurons derived from different progenitors are spatially intermingled. This distribution of clonally related neurons may work as the scaffold to generate the salt-and-pepper architecture observed in rodents. If so, could lineage also account for the architecture of the homogeneous functional columns observed in higher mammals, such as carnivores and primates? The distribution of clonally related cells seems less laterally dispersed and more radially aligned in the monkey cortex, but the complete picture of the progeny of single progenitors has not yet been described. In higher mammals, a large expansion of the subventricular zone has been reported, with each progenitor giving rise to a very large number of neurons through intermediate progenitors. In this scenario, individual cortical stem cells in higher mammals may produce a large cohort of neurons that may comprise an entire functional column with little intermingling of neurons derived from other clones. Alternatively, in higher mammals, each single functional column may be derived from multiple clones, and some mechanisms may group neighboring neurons derived from multiple clones to give rise to their homogeneous functional columns.

(2) Neuronal activity is important for the functional refinement of neuronal circuits in the early visual system. At the level of the cerebral cortex, previous studies have suggested that visual experience contributes to the maintenance and reorganization of

orientation selectivity, but that the initial formation of orientation selectivity is independent of visual experience.

Synchronous spontaneous activity in the developing cortex, partly generated intracortically and partly dependent on retinal activity, has been proposed to be involved in the formation and maturation of orientation selectivity. This synchronous spontaneous activity appears approximately 1 week before eye opening and becomes sparse afterwards. The initial formation and maturation of orientation selectivity is thought to occur during the same period, and this temporal coincidence may imply that the synchronous spontaneous activity is involved in the formation and/or maturation of orientation selectivity. Indeed, a previous report showed that suppressing spontaneous activity by infusing tetrodotoxin (a sodium channel blocker) into the developing visual cortex of ferrets impairs the maturation of orientation selectivity. However, as it is technically challenging to suppress spontaneous activity earlier than the initial formation, its role in the initial formation of orientation selectivity remained untested.

Recently, a genetically specified mechanism has been proposed: cell lineage–derived microcircuit formation is critically involved in the formation of orientation selectivity in the mouse primary visual cortex (V1). Thus, it is still unknown which of the two mechanisms — the activity-dependent or the activity-independent one — is more important for the development of orientation selectivity.

We use a genetic method to suppress neuronal activity starting prenatally, which allow us, for the first time, to investigate the contribution of neuronal activity to the initial formation of orientation selectivity. We observe almost normally tuned orientation selectivity in visual cortical neurons in adults despite a strong suppression of both spontaneous and visually evoked activity throughout development. This finding suggests that the initial formation and maturation of orientation selectivity is largely activity independent (Hagihara et al., 2015).

(3) It has been debated whether orientation selectivity in mouse primary visual cortex (V1) is derived from tuned lateral geniculate nucleus (LGN) inputs or computed from untuned LGN inputs. However, few studies have measured orientation tuning of LGN axons projecting to V1. We measure the response properties of mouse LGN axons terminating in V1 and find that LGN axons projecting to layer 4 are generally less tuned for orientation than axons projecting to more superficial layers of V1. We also find several differences in response properties between LGN axons and V1 neurons in layer 4. These results suggest that orientation selectivity of mouse V1 may not simply be inherited from LGN inputs, but could also depend on thalamocortical or V1 circuits (Kondo and Ohki, 2016).

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# 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, 2 technical staff, 3 postdoctoral researchers, 4 graduate students.

## Teaching activities

The department provides lectures and practice in physiology for undergraduate students. We teach imaging, electrophysiology 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) Thalamocortical dynamics mediate learning and execution of self-initiated movement.

The primary motor cortex (M1) integrates a variety of information from other brain regions and transmits motor commands to the spinal cord. Information from the basal ganglia and cerebellum, which is thought to

be critical for motor learning and motor execution, is signaled to the M1 through the thalamus. However, the temporal dynamics of thalamocortical neural activity during motor learning are poorly understood. To address these issues, we conducted two-photon calcium imaging in mice M1 during learning of a lever-pull task (Hira et al., 2013; Masamizu and Tanaka et al., 2014). We found that thalamocortical axonal activities in M1 evolve their specific representation for movements through the learning and employ various temporal dynamics depending on their projecting layers. The population activity of the thalamocortical axons possessed a lever-relevant sequential structure that was longer in layer 1 than in layer 3 of M1 in the late stage of learning. Our results suggest that the layer 1 and layer 3 thalamocortical dynamics are essential for motor learning and execution.

(2) Development of wide-field two-photon microscopy for simultaneous imaging of multiple cortical areas at cellular resolution.

Understanding the dynamics of cortico-cortical communications is essential because information processing in the brain is not only performed in intra-areal circuits but also through inter-areal interactions. To execute voluntary movements, the interactions between M1 and the secondary motor area (M2) and between M1 and sensory-associated areas are crucial. Recent advances in two-photon microscopy have allowed us to image a relatively large area (up to 1 mm) at cellular resolution. However, it is still difficult to image a continuous large field (>2 mm) and two distant (>3 mm) brain areas at cellular resolution using a single two-photon microscope. We developed super-wide-field two-photon microscopy with a single objective, which allows the imaging of two distant (up to 6 mm apart) cortical areas and a large continuous area (up to 3 mm) at cellular resolution. The method depends on placing a novel optical device under a high-NA objective with a long working distance in a standard two-photon microscope. The device is composed of a pair of mirrors and a holder to rotate the mirrors perpendicular to the optical axis. By controlling the rotation timing and angle using custom-made software, the field of view can be rapidly switched without moving either the objective or the sample.

By rotating the mirror pair back and forth between two angles, we conducted sequential two-photon calcium imaging of neuronal activities in two distant areas up to 6 mm apart and at a depth of up to 800 μm from the cortical surface. Furthermore, by stitching the fields of view, we succeeded in imaging a 3 mm × 1 mm continuous area. We applied it to concurrent calcium imaging of layer 2/3 and layer 5 neurons in M2 and M1 while the mice performed a lever-pull task. We are analyzing how the neural activities in these fields are coordinated during motor execution. Importantly, the optical device together with the controller can be easily installed on a standard two-photon microscope. Its adaptation by neuroscientists should open the door to the study of information processing in brain networks at cellular resolution.

(3) Development of two-photon calcium imaging of the medial frontal cortex without cortical invasion.

*In vivo* two-photon calcium imaging is a fundamental method for understanding the function of neuronal circuits in living animals. The excitation light at infrared wavelengths can penetrate brain tissue deeply, so the excitation volume is very small (<1 μm) and phototoxicity is weak. It is currently possible to observe the activity of multiple neurons at cellular resolution up to ~900 μm from the cortical surface. However, even in the mouse, there are many important brain areas that are located deeper than this. When imaging neural activity from areas such as the medial prefrontal cortex, hippocampus, and striatum, insertion of a lens or aspiration of the upper cortical tissue is necessary. We established a functional calcium-imaging method that allows us to observe neuronal activity at depths of 1000–1200 μm from the pia without any cortical invasion. We combined red genetically encoded calcium indicators and two-photon microscopy with an excitation laser at wavelengths of >1000 nm. Using our procedure, we detected calcium activity from layers 2/3 and 5 of M2 and from the dorsal area of the medial frontal cortex (roughly corresponding to the prelimbic area) in behaving head-restrained mice over several days. We found that the pattern of preparatory activity before

reward acquisition depended on the depth from the cortical surface. Reducing the invasiveness of two-photon calcium imaging is an important strategy for revealing the roles of the medial frontal cortex and other deep brain areas in behaving animals.

(4) Development of marmoset forelimb-movement tasks for two-photon $Ca^{2+}$ imaging of the motor cortex.

Recent advances in calcium imaging have revealed cellular and subcellular mechanisms underlying a variety of brain functions in rodents, fishes, and invertebrates. However, the calcium imaging technique is still difficult to apply to awake non-human primates, especially during forelimb movement tasks, which are very useful for investigating the mechanisms underlying cognitive behaviors, decision making, motor planning/execution and motor skill learning. We have extended the technique of two-photon calcium imaging, which we established in a non-human primate, the common marmoset, in an anesthetized state (Sadakane et al., 2015), to record neuronal activity in the cerebral cortex of behaving marmosets.

To do so, we developed a novel lever-manipulation device with a chair that restrains the head and body, but not forelimbs. Three marmosets were trained with the device 10–60 min per day for 2–3 weeks. The marmosets successfully learned a self-initiated lever-pull task, in which the animals have to pull the lever to get a reward. The marmosets also learned a visual cued lever-pull task, in which the reward is delivered only when the cue is presented on the monitor and the lever is pulled, with additional 1–2 weeks of the training. We conducted two-photon calcium imaging in M1 of the marmosets during the task, using novel marmoset-specific two-photon microscopy, which allows us to observe any dorsal cortical area in marmosets sitting on the chair. We detected calcium transients responding to forelimb movements from somata and dendrites.

Overall, these results indicate that forelimb movement tasks for head-restrained marmosets are feasible and that neural activities can be monitored in the neocortex of behaving marmosets with cellular and subcellular resolution over days by two-photon calcium imaging.

(From abstracts in the 40th 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 5 faculty members (professor, 3 research associate, project research associate), 3 postdoctoral fellows, 12 graduate students, 4 undergraduate students 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 gastrocnemius muscles and learn how the stretch reflex works.

We accept Free-Quarter students. Students are encouraged to experience patch-clamp recordings from neurons either in brain slices or in dissociated 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 approaches including electrophysiology, pharmacology, morphology, and genetic engineering of mouse. We

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

The main subjects of our research are as follows

(1) Refinement of synaptic organization during cerebellar development:

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

(2) Retrograde synaptic modulation mediated by endogenous cannabinoids:

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

(3) Synaptic integration in intact animals:

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

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# Functional Biology

## 2. Pharmacology

# 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 six 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

Our department has a strong background in the field of $Ca^{2+}$ signalling. $Ca^{2+}$ signal is now known to function as a molecular switch in almost every important cell function including muscle contraction, exocytosis, cell proliferation, immune responses and regulation of synaptic functions. This is the reason why this field is expanding rapidly and our research activity is now diversifying. We are particularly interested in $Ca^{2+}$ signalling in the central nervous system.

1) Spatiotemporal regulation of $Ca^{2+}$ signals

$Ca^{2+}$ signals show very dynamic, temporal and spatial changes within the cell. This property allows the $Ca^{2+}$ signal to be an extremely versatile cellular switch regulating diverse cell functions. One of the most notable spatiotemporal patterns of $Ca^{2+}$ signals is the oscillatory change in intracellular $Ca^{2+}$ concentration ($[Ca^{2+}]_i$), or $Ca^{2+}$ oscillation. Many cellular functions are regulated by the $Ca^{2+}$ oscillation frequency. However, fundamental questions remain. How and why does $[Ca^{2+}]_i$ oscillate? We have addressed these questions. First, we studied inositol 1,4,5-trisphosphate ($IP_3$)-induced $Ca^{2+}$ release mechanism, which is one of the most important $Ca^{2+}$ mobilizing mechanisms in many types of cell. We showed that the activity of the $IP_3$ receptor ($IP_3R$) is dependent on the cytoplasmic $Ca^{2+}$ concentration. Therefore, $Ca^{2+}$ release via the $IP_3R$ appears to be under the feedback control of mobilized $Ca^{2+}$. We identified the $Ca^{2+}$ sensor region of the $IP_3R$ and showed that the positive feedback regulation of $IP_3R$ via the $Ca^{2+}$ sensor of $IP_3R$ indeed plays

an essential role in regulating the $Ca^{2+}$ signal dynamics including $Ca^{2+}$ oscillation.

In order to further study the mechanism underlying $Ca^{2+}$ oscillation, we visualized the $Ca^{2+}$ concentrations within the intracellular organelles (both endoplasmic reticulum and mitochondria) during $Ca^{2+}$ oscillations. We found that $Ca^{2+}$ shuttles between these intracellular organelles in phase with cytoplasmic $Ca^{2+}$ oscillations. Our results also indicated that the $Ca^{2+}$ shuttling determines the $Ca^{2+}$ oscillation frequency. Thus, we have shown that mitochondria play an important role in the generation of $Ca^{2+}$ oscillation. These results provide a clue to the mechanism of $Ca^{2+}$ oscillation.

Furthermore, we recently generated a family of genetically-encoded $Ca^{2+}$ indicators named CEPIA (for Calcium-measuring organelle-Entrapped Protein IndicAtors). CEPIA can be used to image ER and mitochondrial $Ca^{2+}$ dynamics simultaneously with cytosolic $Ca^{2+}$ concentration and other cellular processes at high spatiotemporal resolution.

Why then does $[Ca^{2+}]_i$ have to oscillate? Transcription by the nuclear factor of activated T cells (NFAT) is one of the important cellular functions that are regulated by the $Ca^{2+}$ oscillation frequency. NFAT is dephosphorylated by $Ca^{2+}$-dependent phosphatase, calcineurin, and translocates from the cytoplasm to the nucleus to initiate transcription. We analyzed the kinetics of the dephosphorylation and translocation of NFAT, and found that the dephosphorylated form of NFAT functions as a working memory of transient increases in $[Ca^{2+}]_i$. With increasing frequency of $Ca^{2+}$ oscillation, dephosphorylated NFAT accumulates in the cytoplasm to enhance its nuclear translocation. This is the molecular basis of the mechanism that decodes the $Ca^{2+}$ oscillation frequency. We also showed that $Ca^{2+}$ oscillation is more cost-effective in regulating cell functions than a continuous increase in $Ca^{2+}$. These studies provide us with an insight into the secrets of $Ca^{2+}$ signalling.

2) Imaging of signalling molecules

Our study on $Ca^{2+}$ signalling made us realize the importance of visualization of signalling molecules within living cells. Thus, our laboratory has been involved in the generation of new indicators of signalling molecules upstream and downstream $Ca^{2+}$ signals. We have succeeded in imaging $IP_3$ signalling in various cells including intact neurons within cerebellar slice preparations. We also developed an indicator to detect the phosphorylation of myosin regulatory light chain. The indicator allowed us to image phosphorylation state of myosin light chain in living cells. Furthermore, we generated a nitric oxide (NO) indicator based on the heme-binding domain of soluble guanylyl cyclase. This indicator was successfully used in cerebellar slice preparations to image NO signals in response to parallel fiber (PF) stimulation. We found that the NO signal intensity decreases steeply with distance form the activated synapse and generate synapse-specific long-term potentiation (LTP) of PF-Purkinje cell synapses. We also showed that the NO signal intensity depends biphasically on the frequency of PF stimulation. Importantly, the LTP depends similarly on the frequency of PF stimulation. Thus, our NO indicator provided us with valuable information regarding the role of NO signals in the central nervous system.

Glutamate is the most important excitatory synaptic transmitter in the brain. We have generated a glutamate indicator based on the glutamate-binding domain of the AMPA-type glutamate receptor. Using this fluorescent glutamate indicator, we have succeeded in imaging spatiotemporal dynamics of glutamate in the extrasynaptic space in brain slices. 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.

3) Exploration of previously unrecognized cellular functions that are regulated by $Ca^{2+}$ signals

Although many important cell functions have been found to be regulated by $Ca^{2+}$ signals, not all the $Ca^{2+}$-dependent cell functions have been

identified. We are now searching for new cell functions that are regulated by $Ca^{2+}$ signals.

Cells communicate with each other to form organized structures by cell-cell adhesion and cell-cell repulsion, but it remains to be clarified how cell-cell contact information is converted to intracellular signals. We found that cells in contact with neighbouring cells generate local transient intracellular $Ca^{2+}$ signals ($Ca^{2+}$ lightning). $Ca^{2+}$ lightning was exclusively observed near cell-cell contact regions and was not observed in the central regions of cells, nor was it found in solitary cells that are not in contact with other cells. We also show that $Ca^{2+}$ lightning is capable of regulating cell-cell repulsion in a $Ca^{2+}$-dependent manner. These results demonstrated that cell-cell contact information may be transmitted by a new form of $Ca^{2+}$ signal, $Ca^{2+}$ lightning, to regulate intracellular events.

We also clarified a new synaptic maintenance mechanism in the parallel fiber→Purkinje cell synapse in the cerebellum. We have found that there is a retrograde signaling mechanism downstream of metabotropic glutamate receptor-mediated $IP_3$-$Ca^{2+}$ signaling in Purkinje cells, which then generates BDNF (brain-derived neurotrophic factor) that maintains the glutamate-release function of the presynaptic terminal of parallel fibers. This presents a new form of activity-dependent synaptic maintenance mechanism.

We have studied the role of $IP_3$-$Ca^{2+}$ signaling in astrocytes (the most abundant glial cells) and found that it regulates the expression of molecules on the surface of astrocytes that regulate the growth of neurons. Our results indicate that N-cadherin is involved in the regulation of neural growth *in vitro*. Furthermore, we recently showed that $IP_3$-$Ca^{2+}$ signaling in cerebellar astrocytes (Bergmann glia) regulates glutamate transporter levels in Bergman glial cells to maintain glutamate clearance in the mature cerebellum.

In response to brain injury, astrocytes undergo structural and functional changes (reactive astrogliosis). We showed that injury-induced $Ca^{2+}$ responses in astrocytes are important for reactive astrogliosis and also for neuroprotection. We studied the molecular mechanism involved in this reaction, and found that a translational repressor Pum2 is downregulated in a $Ca^{2+}$-dependent manner. We also identified that N-cadherin mRNA is one of the target mRNAs of Pum2. Thus, Pum2 down-regulation induces reciprocal up-regulation of N-cadherin after brain injury. When the *N-cadherin* gene is disrupted in astrocytes, injury-induced astrogliosis and neuroprotection were attenuated. These results clarified the molecular events that are responsible for the astrogliosis and neuroprotection following brain injury.

We have identified a new NO-dependent $Ca^{2+}$ signaling mechanism in central neurons. We found that synaptically released NO *S*-nitrosylates the ryanodine receptor (RyR) to activate $Ca^{2+}$ release through the $Ca^{2+}$ release channel, which we refer to as NO-induced $Ca^{2+}$ release (NICR). NICR is required for the NO-dependent LTP at the parallel fiber-Purkinje cell synapse described above. Furthermore, NICR has a pathophysiological role, and seems to play an important role in NO-dependent neuronal cell death after brain ischemia. This finding suggests that NICR can be a therapeutic target in certain forms of ischemic brain diseases.

We have made it possible to image $Ca^{2+}$ signals in the fine processes of individual astrocytes *in vivo* using transgenic mice that express an ultrasensitive genetically encoded $Ca^{2+}$ indicator, YC-Nano50, in an astrocyte-specific manner. This method allowed us to find a previously unidentified mode of spontaneous astrocytic $Ca^{2+}$ signals, $Ca^{2+}$ twinkles, which are preferentially displayed in fine astrocytic processes in living mice brain. Moreover, a highly sensitive nature of astrocytic fine processes as a sensitive detector of neuronal activity was also revealed.

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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 some 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 are currently 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 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, and are developing technology for the research scheme. In order to produce bi-allelic gene knockout mice without crossing, we improved the design of guide RNAs (gRNAs) used in CRISPR-Cas9 technology and developed the "triple CRISPR method" which simultaneously cuts 3 places in a single targeted gene (Sunagawa et al., Cell Reports 2016). When this technique was applied, it succeeded in producing various kinds of gene knockout mice with extremely high production rate (almost 100%) in the first generation. Furthermore, in order to directly produce knock-in mice without crossing, ~100% ES cell-derived mice (ES mice) were directly prepared from the genome-modified ES cells and used for the following experiments. Using this method, multiple rescue experiments on a circadian clock gene knockout mice (Cry1, Cry2 double-KO mice) were performed regarding over 20 strains, leading to the discovery of important phosphorylation sites and protein structures of the molecule (Ode et al., Molecular Cell 2017). Through these experiments, we showed the efficiency and throughput of the established method which facilitates to create genetically modified mice in just about three months and use them for subsequent analyses (Susaki et al. npj Systems Biology and Applications, 2017).

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

The comprehensive identification of molecular circuits at the organism level also requires accurate (>90%) phenotype analysis. In neuroscience, sleep/wake behavior is an intriguing phenotype, because sleep disorders (e.g., insomnia or hypersomnia) are sensitive and informative symptoms of almost all psychological disorders. Sleep/wake states have been characterized in humans by electroencephalography (EEG) and electromyography (EMG). Characteristic EEG/EMG patterns during sleep and waking are preserved in mammals and can be measured by electrodes surgically implanted in the brain and muscles. However, such recording requires special surgical skills, and the surgery is highly invasive, requiring a long recovery period (more than 10 days) after implantation before sleep/wake recording. Furthermore, the EEG/EMG data are often manually annotated and classified into sleep/wake phenotypes by visual assessment, which can be time consuming and somewhat subjective. Therefore, sleep/wake phenotyping has been a low-throughput method; for comprehensive studies, a scalable, non-invasive, fully automated sleep/wake recording method was needed. For accurate phenotype analysis, we developed a respiration-based, non-invasive, fully automated system, the Snappy Sleep Stager (SSS), which enabled the high-performance analysis (95.3% accuracy) of sleep/wake phenotypes (Sunagawa et al., Cell Reports, 2016).

To highlight the regulatory cellular networks in the sleep/wake rhythm, we facilitate an identification of sleep/wake generating cells in the whole-brain in a highly parallelized manner. A concerted effort has been made especially in the brain, as scientists are aiming to clarify how neural activity is translated into consciousness and other complex brain activities. One example of the technologies needed is whole-brain imaging at single-cell resolution. This imaging normally involves preparing a highly transparent sample that minimizes light scattering and then imaging neurons tagged with fluorescent probes at different slices to produce a 3D representation. However, limitations in current methods prevent comprehensive study of the relationship. A new high-throughput method, CUBIC (Clear, Unobstructed Brain Imaging Cocktails and Computational Analysis), published in Cell, is a great leap forward, as it offers unprecedented rapid whole-brain imaging at single cell resolution and a simple protocol to clear and transparentize the brain sample based on the use of aminoalcohols (Susaki et al., Cell, 2014; Tainaka et al., Cell 2014; Susaki et al., 2015; Kubota et al. Cell Reports 2017; Nojima et al. Scientific Reports 2017). CUBIC provides information on previously unattainable 3D gene expression profiles and neural

networks at the systems level. Because of its rapid and high-throughput imaging, CUBIC offers extraordinary opportunity to analyze localized effects of genomic editing. It also is expected to identify neural connections at the whole brain level.

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 spices shows characteristic different sleep duration. However, detailed molecular mechanisms underlying the control of sleep duration in mammals are still elusive. Using triple-target CRISPR, SSS, and CUBIC techniques, we discover that $Ca^{2+}$-dependent neuronal hyperpolarization pathway affects sleep duration in mammals (Sunagawa et al., Cell Reports 2016; Tatsuki et al., Neuron 2016).

We first focused on the firing pattern of cortex neuron, characterized by alternating bursting and silent phases. This pattern is the basis of slow-wave oscillation observed in EEG recording during slow-wave sleep. We created a computational model that simulates the membrane potential of cortex neuron regulated by a group of ion channels, and found that $Ca^{2+}$ influx into neuron and resultant activation of $Ca^{2+}$-dependent $K^+$ channel is critical for the emergence of alternating bursting and silent phases.

For the experimental verification of this prediction, we created a series of knock-out mice using the triple-CRISPR method and analyzed their sleep phenotype by SSS. We found that knocking out of following ion channels results in significant short sleep duration; *Cacna1g*, *Cacna1h* (voltage-dependent calcium channel), *Kcnn2*, *Kcnn3* (calcium-dependent potassium channel), *Nr3a* (NMDA receptor). On the other hand *Atp2b3* (plasma membrane calcium-transporting ATPase) knock-out mice showed increased sleep duration. Overall, these results suggest that pathways for calcium influx and calcium-dependent channels/kinases contribute to increase sleep duration, while the antagonizing calcium export pathway contributes to decrease sleep duration.

We further verified the role of NMDA receptors by pharmacological inhibition of the receptor, because the knocking out of some NMDA receptor subtypes (*Nr1* or *Nr2b*) leads to embryonic lethality. As expected, administration of NMDA receptor antagonist shortens the sleep duration. We then observed an expression-pattern of marker protein for neuronal excitability in a whole-brain scale with the CUBIC method, and revealed that the antagonist administration resulted in the elevated excitability of cortex pyramidal neurons. This observation consistent with our hypothesis that $Ca^{2+}$ influx reduces the excitability of cortex neuron through the hyper polarization of membrane potential.

Given these results showing the role of $Ca2^{+}$ for sleep control, our next challenge is to investigate molecules that regulate the transition between sleep and awake phases. We focused on CaMKII (calcium/calmodulin-dependent protein kinase II), protein kinases important for the post-translational regulation of several neuronal channels. We found that *Camk2a* or *Camk2b* knock-out mice exhibit abnormal sleep phenotype. These kinases may play an important role for the transition between neural activities, which happen during milliseconds to seconds, and exchange of sleep/awake states, which occurs in a time scale of minutes to hours (Tatsuki et al., Neurosci. Res. 2017; Ode et al., Curr. Opin. Neurobiol. 2017).

We further revealed the mechanism of temperature compensation in circadian clock. The biological clock regulates 24h animal behavior including sleep and wake. We investigate biochemical mechanisms underlying temperature-compensated, CKIδ-dependent multi-site phosphorylation in mammals. We identify two mechanisms for temperature-insensitive phosphorylation at higher temperature: lower substrate affinity to CKIδ-ATP complex and higher product affinity to CKIδ-ADP complex. Our findings suggest the temperature-sensitive substrate- and product-binding mechanisms underlie temperature compensation of circadian clock.

Considering that numbers of researches encompass model mice for sleep, circadian rhythm and related disorders, we envisage that our technologies and research outcomes will contribute the understanding

of such disorders including psychiatric disorders and neurodegenerative disorders.

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# Pathology, Immunology and Microbiology

## 1. Pathology

# Department of Pathology and Diagnostic Pathology

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## Introduction and Organization

Department of Pathology and Diagnostic Pathology is responsible for the practice of diagnostic pathology, education, and research in conjunction with Division of Diagnostic Pathology of the University Hospital*. Our aim is the construction of "pathology as clinical medicine" as well as "next-generation pathology incorporating cutting-edge science and technology".

Associate Professor Dr. Shibahara moved as the chairman and professor to Department of Pathology, Kyorin University, School of Medicine. Lecturer Dr. Morikawa was promoted to the associate professor, and lecturer (Hospital) Dr. Aya Ushiku to the lecturer*, respectively. Dr. Atsushi Tanaka and Dr. Zen-ichi Tanei were now Associates.

Three postgraduate students (Saito, Hinata, Mine) finished the course and received Ph.D. In the new fiscal year, 2017, six new students will enter the postgraduate course, and there will be 21 postgraduates.

We are responsible for the pathology practice of the University Hospital, and are carrying forward the morphology-based research targeting human diseases.

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

To promote genomic medicine in clinical care, we set up Center for Genome Pathology Standardization (assisted by Japan Agency for Medical Research and Development). The mission of the Center is to investigate basic technologies for tissue banking, and to hold seminars for doctors and technicians (see the section of Diagnostic Pathology Division). Clinical Genome Conference started in the University of Tokyo Hospital for the application of cancer clinical sequencing to medical practice as a research project of genome medicine (Project organizer: Prof. Hiroyuki Mano).

We will join the research project of Japanese Society of Pathology "Database of Pathology-Whole Slide Image (WSI) for Development of Artificial Intelligence (AI) Technique and AI-based Support System for Pathology Diagnosis" in 2017.

## Clinical activities (diagnostic pathology and autopsy)

Together with Division of Diagnostic Pathology, we are responsible for the pathologic diagnosis and autopsy in the University Hospital. We set up Telepathology & Remote Diagnosis Promotion Center (TRD-PC), and started Outpatient Clinic of Pathology (see the corresponding section of Division of Diagnostic Pathology).

Surgical pathology conferences are regularly held with each clinical division, and the cases of various tumors are discussed, including thoracic organs, liver and pancreato-biliary tract, urology, gynecology, breast, and orthopedics, as well as biopsy cases of kidney, and skin.

Clinico-pathological conferences (CPCs) for two autopsy cases are held every month in the hospital. Both CPCs and weekly autopsy conferences are useful for the education of clinical residents. Digest versions of CPC slides are now open in the hospital (Drs. Shintani and Hayashi), and we also started e-learning programs for clinical residents to facilitate the understanding of the CPC contents (Dr. Ikemura). All of residents were obligated to take the course for their training once a year.

A model project for the survey analysis of deaths related to medical treatment (DRMT) started from September 2005, and finished at the end of 2015 fiscal A new system for evaluation of deaths related to medical treatment (DRMT) started from October, 2016.

## Teaching activities

We take on General Pathology Course for the 1st grade of undergraduate students, especially in its morphological 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 pathological 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 4th grade medical students, following courses are included; autopsy pathologic practices with a case presentation for paired students, surgical pathologic practices using various tumor sections, and a tour of the pathology laboratory.

Four students chose the clinical clerkship course for 3rd grade medical students. As for the free quarter program, we received two and five students of M0 and M1, respectively, in this fiscal year.

We also set up the lecture series of "Infection/ Immunology/Cancer II" and "Tumor Pathology. We also provided two intensive exercise courses, "Integration of Neuropathology/Raiology/Clinics" and "Histochemistry/Immuno-histochemistry/Clinical Electron Microscopy".

## Research activities

The first major theme is "chronic inflammation and neoplasms", especially Epstein-Barr virus (EBV) associated gastric carcinoma (GC) (Drs. Kunita, Shinozaki-Ushiku and Abe). We focused on the immune-escape mechanism of EBV-associated GC

this year (ref.1,7). We revealed that PD-L1 is frequently expressed in cancer cells of EBV-associated GC (ref.30). Furthermore, gene amplification of PD-L1 occurs in some of them. We investigated the relationship of H. pylori infection (ref.31) and molecular mechanism of epigenetic abnormalities (ref.24) in this specific type of gastric cancer.

The second major theme is 'translational research pathology'. We are engaged in search of target molecules for cancer therapy by global analysis of various cancers, in collaboration with Research Center for Advanced Science and Technology (RCAST) (Drs. Ushiku and Morikawa) (ref.20,22). We developed a new diagnostic technique (ref.21) and evaluated therapeutic effect (ref.43) for the molecular target therapy.

The third theme is to re-evaluate the disease entities and tumor entities from the standpoint of histopathology. Dr. Sibahara proposed Type 1/2 system for the classification of intrahepatic cholangiocarcinoma (ref.4-6), and reassessed the subset of hepatocellular carcinoma (ref.33). We also performed investigation of gastric cancers (ref.29, 43), brain tumor (ref.10) and leukemia (ref.45).

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(including those of Diagnostic Pathology Division)
Case reports are listed in the section of Diagnostic Pathology Division.


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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. Prof. Miyazono is Professor of the Department of Molecular Pathology from August 2000. In March 2017, the Department consists of a professor, an associate professor, a project associate professor, two assistant professors, technical assistants, and some research fellows, including 5 graduate students, a master course student, four post-doctoral fellows, and a guest scientist.

## Teaching activities

Our department takes responsibility for lectures on "General Pathology" for the 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 at this floor. We have "Progress Meeting" twice a month and "Monday Seminar" once a month.

Prof. Kohei Miyazono organized the 75th Annual Meeting of the Japanese Cancer Association as the chairman from October 6 to 8 at Pacifico Yokohama. Nearly 5,000 participants attended the meeting, and exchanged their research findings.

From 2015, our research projects are mainly supported by a Grant-in-Aid for Scientific Research (S) on "Transcriptional regulation by TGF-β signaling and its relation to progression of cancer" from the Japanese Society for the Promotion of Science (JSPS).

We have been doing collaboration with the Ludwig Institute for Cancer Research, Uppsala, Sweden for more than 20 years (http://c2ctgfb.umin.jp/). We have annual TGF-β meeting in Sweden or in the

Netherlands every year, and three graduate students participated in the TGF-β meeting in Leiden in 2016.

Four of our graduate students are 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). GPLLI was designed for the purpose of guiding outstanding students to be globally active leaders in industry, academia and government. This program also stimulates interaction between students and scientists in the program as well as those from other laboratories (http://square.umin.ac.jp/gplli/).

## Research activities

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

*Ras and TGF-β signaling coordinately enhance cancer progression by promoting the p63 transcriptional program:* TGF-β-induced cellular responses are known to be determined by cooperatively acting signaling cascades, including integrin, Notch, Wnt, and EGF signals. Among the various signaling pathways acting in concert with TGF-β, synergy between TGF-β and Ras/Erk MAP kinase signaling has been extensively studied. We and others have previously reported that activation of both TGF-β and Ras/Erk MAP kinase pathways enhances the migratory and invasive properties of epithelial cells through synergistic induction of epithelial-mesenchymal transition (EMT).

To identify the downstream effectors of the synergistic action of TGF-β and Ras/Erk MAP kinase pathways, we focused on p63, a member of the p53 family of transcription factors and one of the master regulators of epithelial cell differentiation and migration. Two different isoforms of p63, TAp63 and ΔNp63, have been reported to show opposing functions. TAp63 contains the N-terminal transactivation (TA) domain, while ΔNp63, an N-terminal truncated isoform, lacks the TA domain. ΔNp63 is an amino-terminally truncated isoform, and the predominant isoform expressed in cancer cells of epithelial origin. We have determined the genome-wide binding landscape of p63 in combination with gene expression profiles in the presence and absence of TGF-β stimulation and Ras/Erk MAP kinase activation in HaCaT human keratinocytes, which have mutant p53 and ΔNp63. We found that mutant p53 antagonized ΔNp63 transcriptional activity, but that activation of Ras or TGF-β signaling pathways reduced the amounts of mutant p53 protein, leading to higher target gene binding of ΔNp63. Among the target proteins of ΔNp63-induced genes, we found that dual-specificity phosphatase 6 (DUSP6) promoted the degradation of mutant p53, possibly through dephosphorylation of p53. Knocking down the expression of p63 or DUSP6 and DUSP7 (DUSP6/7) inhibited the basal or TGF-β-induced or EGF/Ras-induced migration and invasion of p53-mutant breast cancer and squamous skin cancer cells. On the other hand, overexpression of ΔNp63 in the breast cancer cells increased their ability to form metastatic foci at various tissues upon intracardiac injection in mice, and this was inhibited by knocking down the expression of DUSP6/7 in these cells overexpressing ΔNp63. High expression of ΔNp63 in various tumors correlated with poor prognosis in patients, and this correlation was stronger in patients whose tumors also had a mutation in the *TP53* gene. Thus, oncogenic Ras and TGF-β signaling coordinately stimulate progression of cancer through activation of the ΔNp63 transcriptional program (Vasilaki et al. *Science Signaling* 2016).

*Dual targeting of VEGF and BMP-9/10 impairs tumor growth through inhibition of angiogenesis:* Tumor microenvironment is composed not only of cancer cells but also of various types of stroma cells including tumor vessels, which determine characteristics of tumor tissues. Tumor vessels provide oxygen and nutrient with cancer cells, and become main routes for cancer cells to metastasize to distant organs. Therefore, it is crucial to develop effective strategies to target angiogenic signals in order to inhibit tumor growth and metastasis. Signals mediated by vascular endothelial growth factor (VEGF) have been implicated in tumor angiogenesis. In addition, we have previously reported that BMP-9 promotes multiple types of angiogenesis, including tumor

angiogenesis, by stimulating the proliferation of endothelial cells. BMP-10 is structurally similar to BMP-9 and transduces signals through a similar mechanism. Previous studies have demonstrated that targeting the individual signals was not sufficiently effective in suppression of tumor growth in certain conditions. We have developed a novel decoy chimeric receptor which binds both VEGF and BMP-9/10. Although single targeting of either VEGF or BMP-9/10 signals reduced the formation of tumor vessels in a mouse xenograft model of human pancreatic cancer, it did not exhibit significant effects on tumor growth. In contrast, dual targeting of the angiogenic signals by VEGF and BMP-9/10 led to more significant inhibition of tumor angiogenesis, leading to delay of tumor growth. Thus, simultaneous blockade of VEGF and BMP-9/10 signals may be more effective in targeting tumor angiogenesis, and is a promising therapeutic strategy for the cancers that are resistant to anti-VEGF and BMP-9/10 therapies (Akatsu et al. *Cancer Science* in press).

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# Pathology, Immunology and Microbiology

## 2. Microbiology

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## Introduction and Organization

Professor emeritus Akio Nomoto who had been the chief of the Department retired in 2008 and moved to Microbial Chemistry Research Foundation as the Chairman of Board. From 2009, new Department of Microbiology started with Professor Masanori Hatakeyama as the new chief. The present Department consists of 18 members; 1 professor (Dr. Hatakeyama), 1 senior lecturer (Dr. Kamiya), 2 research associates (Drs. Takahashi and Hayashi), 1 project research associate (Dr. Fujii), 2 post-doctoral fellows (Drs. Nishikawa and Kikuchi), 2 academic assistants (Ms. Shimada and Komatsu), 10 graduate school students (Ms. and Mrs. Hashi, Bingo, Ohki, Nojima, Ben, Lu, Knight, Inoue, Imai).

## Education

In a series of lectures (totally 64 hr) and laboratory courses (36 hr), the following subjects are covered.

1) Molecular biology of bacteria, phages, and animal viruses
2) Mechanisms of microbial diseases
3) Laboratory diagnosis of pathogenic microbes
4) Infection control and biosafety
5) Application of microbial organisms for bio-technology
6) Socioeconomic impact of microbial diseases

## Research

Gastric cancer is the second 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 of *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. Collaboration between *cagA*-positive *Helicobacter pylori* and Epstein-Barr virus in gastric carcinogenesis**

Most if not all human gastric cancers are caused by chronic infection of the stomach lining with *H. pylori* strains that possess the *cagA* gene. Approximately 10% of gastric cancer cases also harbor Epstein-Barr virus (EBV) in the cancer cells. Upon delivery into gastric epithelial cells via type IV secretion, CagA undergoes tyrosine phosphorylation by Src family kinases or c-Abl kinase at the Glu-Pro-Ile-Tyr-Ala (EPIYA) motif. Tyrosine-phosphorylated CagA binds to the pro-oncogenic protein tyrosine phosphatase SHP2 and thereby aberrantly activates the phosphatase activity, which has been considered to play an important role in gastric carcinogenesis.

We identified SHP1, the only homologue of SHP2, as a tyrosine phosphatase that dephosphorylates CagA. We showed that SHP1 interacts with CagA independently of EPIYA motif. The interaction potentiates the phosphatase activity of SHP1 that subverts the oncogenic activity of CagA by dephosphorylating the CagA EPIYA motifs. These observations indicated that the level of SHP1 in gastric epithelial cells influences the magnitude of CagA action.

EBV-positive gastric cancers are associated with genome-wide hypermethylation. Since the most of patients with EBV-positive gastric cancer are co-infected with *H. pylori*, we investigated the methylation status of *SHP1* (*PTPN6*) in gastric epithelial cells. *In vitro* infection of gastric epithelial cells with EBV induced *SHP1* promoter hyper-methylation, which reflected the decrease of *SHP1* mRNA and SHP1 protein expression. Further more, phosphorylation-dependent CagA activity was substantially strengthened in EBV-positive gastric epithelial cells. Clinical specimens of EBV-positive gastric cancers also exhibited SHP1 hypermethylation with reduced SHP1 expression. This work revealed that a pathophysiological collaboration between the *H. pylori* bacterium and the EBV cooperate in promoting the development of gastric cancer.

**2. Impact of structural polymorphism for the *Helicobacter pylori* CagA on binding to polarity-regulating kinase PAR1b**

Once inside the host cells, *H. pylori* CagA also binds to partitioning-defective 1b (PAR1b)/microtubule affinity-regulating kinase 2 (MARK2) via the CagA multimerization (CM) motif in a tyrosine phosphorylation-independent manner. Through complex formation, CagA inhibits kinase activity of PAR1b, resulting in induction of junctional and polarity defects. Notably, the polymorphism in the CM motif has been identified among geographic variants of CagA, differing in either the copy number or the sequence composition.

Through quantitative analysis of the complex formation between CagA and PAR1b, we found that several CagA species have acquired elevated PAR1b-binding activity via duplication of the CM motifs, while others have lost their PAR1b-binding activity. We also found that strength of CagA-PAR1b interaction is proportional to the degrees of stress fiber formation and tight junctional disruption by CagA in gastric epithelial cells. These results indicate that the CM polymorphism is a determinant for the magnitude of pathophysiological actions of *H. pylori* CagA. Therefore, the CM diversity may contribute to the different disease manifestations caused by *cagA*-positive *H. pylori* infection.

**3. Pragmin-Csk interaction creates a positive feedback regulatory loop of Csk activation that regulate cell motility**

Inside the host cells, tyrosine-phosphorylated CagA binds to SH2 domain-containing mammalian proteins such as SHP2 and the C-terminal Src kinase (Csk), a negative regulator of Src family kinases. Pragmin is one of the few mammalian proteins that possess the Glu-Pro-Ile-Tyr-Ala (EPIYA) motif. Like CagA, Pragmin also forms a physical complex with Csk.

In the present study, we found that Pragmin directly binds to Csk by the tyrosine-phosphorylated EPIYA motif. The complex formation potentiates kinase activity of Csk, which in turn phosphorylates Pragmin on tyrosine-238 (Y238), Y343, and Y391. As Y391 of Pragmin comprises the EPIYA motif, Pragmin-Csk interaction creates a positive feedback regulatory loop of Csk activation. We also found that Pragmin and Csk

are colocalized to focal adhesions. These observations indicate that the Pragmin-Csk interaction, triggered by Pragmin EPIYA phosphorylation, robustly stimulates the kinase activity of Csk at focal adhesions, which direct cell-matrix adhesion that regulates cell morphology and cell motility. As a consequence, expression of Pragmin and/or Csk in epithelial cells induces an elongated cell shape with elevated cell scattering in a manner that is mutually dependent on Pragmin and Csk. Therefore, deregulation of the Pragmin-Csk axis may induce aberrant cell migration that contributes to tumor invasion and metastasis.

**4. Parafibromin is a transcriptional coactivator of the Wnt/Hedgehog/Notch pathways**

The Wnt, Hedgehog (Hh) and Notch signaling pathways are among only a handful of evolutionally conserved morphogen pathways mediating embryonic development as well as homeostasis of adult tissues. Nevertheless, mechanisms that intracellularly coordinate these signal inputs remain poorly understood.

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. Here we found that parafibromin competitively interacts with β-catenin and Gli1, thereby potentiating transactivation of Wnt- and Hh-target genes in a mutually exclusive manner. Parafibromin also binds to the Notch intracellular domain (NICD), enabling concerted activation of Wnt- and Notch-target genes. 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. Consequently, acute loss of parafibromin in mice disorganizes the normal epithelial architecture of the intestine, which requires coordinated activation/inactivation of Wnt, Hh and/or Notch signaling. This work revealed that multiple independent morphogen signaling pathways converge on the transcriptional platform parafibromin.

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## Introduction and Organization

The Department of Infection Control and Prevention started at first as the Division of Hospital Infection Control Services on January 23, 1991. This division developed into the Division of Infection Control and Prevention on September l, 1993 and the present department on June 4, 1994. Currently, our faculty consists of one professor, six research associates, 11 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 such as mupirocin and vancomycin.
3) Microbiological investigation of wards and environment (at request or need).
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 defences to microorganisms
8) Molecular analysis of innate immunity in micro-organism infection
9) New detection method and pathogenesis of opportunistic cytomegaloviral infection
10) Mechanism of multi-drug resistant micro-organisms
11) Epidemiology of *Clostridium difficile* infection

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# Pathology, Immunology and Microbiology

## 3. Immunology

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## Introduction and Organization

The history of the Department of Immunology, formerly the Department of Serology, dates back to 1918. The department adopted its present name when Dr. Tomio Tada took his position as professor and chair in 1977. Through his innovative research and great contributions to the international community of immunologists, Dr. Tada raised the stature of the department to a world-renowned status. After Dr. Tada's retirement in 1994, Dr. Tadatsugu Taniguchi, presently the designated professor of the Department of Molecular Immunology at the Institute of Industrial Science, the University of Tokyo, performed cutting-edge, internationally recognized research in the field of immunology especially cytokine systems in the context of the regulation of immunity and oncogenesis. Dr. Taniguchi's major achievements were the discovery of interferon-β and a new family of transcription factors, termed interferon regulatory factors (IRFs).

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

## Teaching activities

All members of our department take very seriously their responsibilities to teach and train the next generation of scientists. Undergraduate students of the faculty take part in departmental class work through lectures on immunobiology, immunochemistry and molecular immunology as well as practical training by way of laboratory courses on basic immunology experimental techniques. The education of graduate students is based on weekly seminars where students present the progress of their own research projects, discuss the future directions of their research and the research of others, and are exposed to the latest cutting-edge questions confronting the research field of immunology. We also offer a special training course (called 'free quarter') of basic and advanced biological and immunological techniques to medical students. We are also accepting undergraduate students as Medical Scientist Training Program in faculty of medicine. In fiscal year 2016, special lectures for undergraduate students were given by internationally recognized scientists, Dr. Takehiko Sasazuki (Prof. of Kyushu Univ.), Dr. Shimon Sakaguchi (Prof. of Osaka Univ.), Dr. Hajime Karasuyama (Prof. of Tokyo Medical and Dental Univ.), and Dr. Tadatsugu Taniguchi (Prof. of the Univ. of Tokyo).

## Research activities

The final goal of our research is to develop epoch-making strategies for the treatment of immune disorders such as autoimmune diseases and severe infectious diseases. At the present moment, knowledge in this field, especially about the molecular mechanisms of immune tolerance are quite limited. Therefore, initially, we aim to achieve further understanding about whole immunity, including hematopoietic cell development and regulation of both innate and adaptive immune systems.

1) Bone marrow microenvironment

The bone marrow is a primary lymphoid organ that plays a critical role in immune cell development. It has been proposed by several groups that marrow resident non-hematopoietic cells i.e. osteoblasts, endothelial cells, neurons or reticular cells (named CXCL12 expressing CAR cells) play critical roles on hematopoiesis. However, the crucial cell types that support hematopoietic cell development in the bone marrow have not been clarified.

Recently we reported the crucial role of osteoblasts in supporting lymphoid lineage development within the bone marrow microenvironment (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.

2) Osteoclast and osteoimmunology

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). We also found that immune complexes in serum activate osteoclastogenesis and cause bone loss through binding to Fcγ receptors (Negishi-Koga et al., Nat Commun. 2015).

We also reported that, using a bone-fracture model in mouse, the cytokine IL-17 promotes bone fracture healing via osteoblastic bone formation and that γδT cells are the major source of IL-17 produced in the bone injury site (Ono et al., Nat Commun. 2016). Although it has been known that IL-17 enhances osteoclastic bone resorption in certain pathological situations, our current results clearly show the promoting effect of IL-17 on bone formation, providing a new paradigm for physiological inter-action between bone and immune system.

Most recently, we studied on the physiological significance of lysil oxidase (LOX), the enzyme which was previously reported to induce 'RANKL-independent' osteoclast differentiation (Tsukasaki et al., J Bone Miner Res. 2017). Our results demonstrated that LOX failed to substitute for

RANKL in inducing osteoclastogenesis in vivo, while LOX facilitated the osteoclast differentiation by inducing RANKL expression in bone marrow stromal cells.

3) Development and regulation of lymphoid cells

Thymus is the primary lymphoid organ that supports development of useful T cells (positive selection) and eliminates self-reactive T cells (negative selection). However, recently it has been shown that a fraction of self-reactive T cells escape negative selection in the thymus. This process is called “agonistic selection”. We uncovered importance of continuous calcium influx into cytoplasm for agonistic selection of T cells especially regulatory T cells and iNKT cells (Oh-hora et al., Immunity. 2013). The microenvironment of the thymus is mainly composed of thymic epithelial cells (TEC) that regulate selections of developing T cells (Nitta et al., Adv Immunol. 2008; Nitta and Suzuki, Cell Mol Life Sci. 2016). Using a newly established mouse model of TEC deficiency, we showed the significant role of thymic epithelial cells in development, not only of “conventional” αβT cells but also of inflammatory “innate” γδT cells (Nitta et al., EMBO Rep. 2015).

In the mucosal tissues such as gut and lung, the newly identified innate lymphoid cells (ILCs) play important roles in pathogen clearance, tissue homeostasis, and regulation of immune responses (Sawa et al., Science. 2010). We are trying to understand the cellular and molecular mechanisms that underlie development and function of ILCs. We also aim to identify gut-associated lymphoid tissue stromal cells that control intestinal immunity against commensal and pathogenic microorganisms.

4) Mechanism of autoimmune disease

The IL-17 producing helper T cell subset (Th17 cell) plays critical roles in several autoimmune disease models such as collagen induced arthritis (CIA) and experimental encephalomyelitis (EAE). We have identified IκBζ as an indispensable transcription factor for Th17 cell differentiation (Okamoto et al., Nature. 2010). However, in both RA and EAE models, effector mechanisms of Th17 cells have been unclear. Recently, we identified a subset of Th17 cells that robustly produces IL-17 and RANKL and exacerbates both inflammation and bone destruction in CIA mice. Interestingly these Th17 cells are the progeny of CD4 T cells expressing Foxp3, a master regulator for immunosuppressive Treg cells (Komatsu et al., Nat Med. 2014). We also reported that RANKL produced by synovial fibroblasts is primarily responsible for the formation of bone-destructive osteoclasts in inflammatory arthritis. 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. 2015).

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 and cardiologists 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 nuclear medicine physicians and cardiologists.

Each year, over 700 new patients receive radiation therapy in the Radiation Oncology section. Highly

accurate 3D radiation therapy is the most outstanding feature. Stereotactic radiation therapy for small lung or liver tumors has been carried out.

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

## Teaching activities

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

## Research activities

Research activities in our department include clinical research, animal experiments and development of instruments as well as computer-based new technology. 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 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 tensor 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 was active in studies of the physical engineering traditionally and took 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 and the development of radio-immunotherapy (RIT) 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 [O-15] $H_2O$, $CO_2$, $O_2$, CO, [F-18] FDG, [C-11] methionine, [F-18] Dopa, [C-11] NMSP, NMPB, [C-11] raclopride and [C-11] PiB. 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 PET 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, [N-13] $NH_3$, 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 XCT/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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# Radiology and Biomedical Engineering

## 2. Biomedical Engineering

# Department of System Physiology

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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 one 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 adrenomedulin and C-type natriuretic peptide mRNA which have vasodilating effects in addition to nitric oxide, and that it also augmented the expression of lectin like low density lipoprotein receptor (LOX-1) at the protein and mRNA level.

## 2. Hemodynamic force-mediated gene regulation

We have demonstrated that shear stress regulates endothelial gene expression transcriptionally and/or posttranscriptionally. Shear stress downregulates VCAM-1 gene transcription via the double AP-1 binding element (TGACTCA) in the promoter which functions as a shear stress-responsive element. Shear stress has also been shown to increase the expression level of granulocyte/macrophase-colony stimulating factor (GM-CSF) via mRNA stabilization. Differential display and DNA microarray analysis showed that around 600 known and unknown transcripts were up- or down-regulated in human umbilical vein ECs exposed to a shear stress. From these shear stress-responsive genes, a cDNA encoding an unknown G-protein coupled receptor was cloned. We showed that the transcription factor SP1 is involved in the shear stress-induced down-regulation of P2X4 (an ATP-gated cation channel) gene expression in ECs. We also revealed that endothelial genes are differentially regulated by laminar and turbulent shear stress. Laminar shear stress decreases the gene expression of urokinase plasminogen activator (uPA), which plays a role in fibrinolysis and vascular remodeling, via both GATA6-mediated down-regulation of gene transcription and an acceleration of mRNA degradation, while turbulent shear stress increases the uPA gene expression through mRNA stabilization. We demonstrated that shear stress up-regulates the gene expression of plasminogen activator inhibitor-1 (PAI-1) through activation of transcription factors Sp-1 and Ets-1 in human hepatocytes. We developed a compliant tube-type flow-loading device that allows simultaneous application of physiological levels of shear stress and cyclic strain to cultured cells and observed that the response of endothelial genes to shear stress or cyclic strain depends on whether the two forces are applied separately or together.

## 3. Hemodynamic force-induced cell differentiation

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

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

## 4. Mechanosensing and mechanotransduction

We were the first to show that $Ca^{2+}$ signaling plays an important role in the mechanism by which ECs recognize the shear stress signal and transmit it into

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

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

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# Department of Chemical Biology and Molecular Imaging

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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 2 post-doctoral researchers, 7 PhD students, 2 master course student and one technical staff by the end of FY2016.

## Teaching activities

As for under-graduate education, our laboratory takes part in medical engineering lectures for the 3rd year medical students. As for PhD course education, our laboratory delivers the lecture of fluorescence imaging for both master and doctor course students. Our laboratory is also accepting Free Quarter students every year for the opportunity to be trained to synthesize chemical probes and observe live cells with fluorescent microscopes. Our laboratory is also accepting under-graduate students as Medical Scientist Training Program in faculty of medicine. They are doing their own research under the supervision of our staffs, and one student was graduated this program by the end of FY2016.

## 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 mechanism such as intramolecular spirocyclization. In FY2016, we have succeeded to develop several novel fluorescence probes for visualizing biological analytes or enzyme activities in living cells and tissues.

For example, a reversible fluorescent probe for glutathione was developed based on the mechanism of intermolecular nucleophilic addition/dissociation of glutathione to the fluorophore. This probe enables live-cell imaging and quantification of intracellular glutathione, and real-time monitoring of fast glutathione dynamics. Therefore, it is expected to serve as a practical analytical tool for investigating biological functions of glutathione in living cells (Reference 2).

We also developed a fluorogenic β-galactosidase substrate suitable for labeling live cells in culture, as well as in living tissues. This precisely functionalized fluorescent probe exhibited dramatic activation of fluorescence upon reaction with the enzyme, remained inside cells by anchoring itself to intracellular proteins, and provided single-cell resolution (Reference 4).

We also applied our fluorescence probe library targeted for aminopeptidases and glycosidases to clinical specimens resected from cancer patients, in order to elucidate characteristic features of live cancer cells and to screen a suitable probe for visualizing specific cancer. As a result, we found that our probe for dipeptidylpeptidase IV (DPPIV) is useful for rapid visualization of early esophageal squamous cell

carcinoma in collaboration with Department of Gastrointestinal Surgery, The University of Tokyo Hospital (Reference 7). We also found that a probe for hexosaminidase can visualize human colorectal cancer by collaborating with Department of Surgical Oncology, The University of Tokyo Hospital (Reference 9), and that a probe for γ-glutamyltranspeptidase (GGT) can visualize primary lung cancer with sensitivity of 43.8% and specificity of 84.9% by collaborating with Department of Thoracic Surgery, The University of Tokyo Hospital (Reference 8). We are now validating these new probes for the clinical application.

We also demonstrated that our fluorescence probes with suppressed fluorescence quantum yields are useful for photoacoustic imaging (Reference 1).

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# Department of Biosystem Construction & Control

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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 an associate professor, a lecturer, two project researchers, 7 graduate students, 17 visiting researchers, a senior technical specialist, and a project academic support stuff.

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 to the weekly 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 emergency life support system (ELSS) that is a compact and transportable heart and/or lung assist device has been started in 2004. The device consists of a blood pump, an oxygenator, a drive and control unit, and a battery unit. To realize several-months support with the ELSS, a new blood pump named the sequential flow pump (SFP) has been developed. The SFP in which fluid is given centrifugal force sequentially twice in a pump was invented in our laboratory in 2013. This sequential pressurization mechanism enables high-pressure output without high impeller speed, which can reduce the sheer stress of the blood. To realize integration of the pump with the artificial lung, inlet and outlet ports are located at lateral side and center of the pump, respectively, which is the reverse configuration of conventional centrifugal pumps. In the ELSS, the whole system components will be packed in a case having 180 mm in diameter and 390 mm in length. The whole weight will be about 20 kg.

Our research of the application of ICT (Information and communication technology) to medicine has been focused on the home medical care. The research and development for monitoring the condition of the patients living at home has been performed utilizing the miniaturized wireless electrocardiogram (ECG) unit with low power consumption. The ECG unit is attached on the patient's chest at home. The ECG data is transmitted to the laptop computer set in the patient's home. The data is then transmitted to the data server set at our laboratory through the mobile Internet communication. The client computers in the clinic or doctor's smart phone receive the real-time data through the Internet lines from the data server. This system has been tested experimentally in a clinic. The system revealed to be very useful especially for taking care of the patients who were going to be in deathbed. To obtain more detailed diagnosis of such patients, a breathing monitor is necessary. The transmitter unit contains a three-axis acceleration sensor that is used usually for detecting the motion or posture of the patient. We detected the respiratory frequency using the three-axis acceleration sensor contained in the unit.

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# Neuroscience

## 1. Basic Neuroscience

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

1. Research on β-amyloid and presenilins

Using C-terminal specific monoclonal antibodies that discriminate amyloid β peptides (Aβ) ending at 40th or 42nd residues (Aβ40 and Aβ42, respectively), Dr. Iwatsubo has performed a systematic immuno-histochemical studies on autopsied brain tissues from patients with AD, Down syndrome and familial AD, and demonstrated that Aβ42, that most readily form amyloid fibrils in vitro, is the initially and predominantly deposited species in human cerebral β-amyloidosis (Iwatsubo et al. Neuron 1994, Ann Neurol 1995). Dr. Iwatsubo's group then established celllar models expressing mutant forms of presenilin (PS) genes linked to familial AD (FAD), and using their original highly-sensitive ELISA quantitation system, his group has clearly shown that an increase in the production of Aβ42 is the pathogenic mechanism leading to FAD (Tomita et al. Proc Natl Acad Sci USA, 1997). These findings have provided a firm basis for the currently prevailing β-amyloid hypothesis. They then focused on the mechanisms of γ-secretase complex that cleaves the C terminus of Aβ, and set out to cell biological studies using RNA interference on the formation and function of the γ-secretase complex harboring PS as the catalytic center, associated with three additional membrane proteins. They demonstrated that APH-1 and Nicastrin serve as the "stabilizing" co-factor of PS, whereas

PEN-2 is the component that confers proteolytic activity to this complex. They also showed that PS, APH-1, nicastrin and PEN-2 are the essential set of proteins that comprise the γ-secretase complex (Takasugi et al. Nature, 2003). This study is highlighted as a milestone work that elucidated the mechanistic roles of protein cofactors in the formation and function of γ-secretase (see reviews; Iwatsubo Mol Psychiatr, 2004; Curr Opin Neurobiol, 2004). His group has also shown by establishing in vitro γ-secretase assays that sulindac sulfide, a major non-steroidal anti-inflammatory drugs, directly acts on γ-secretase and selectively reduce Aβ42-generating activities (Takahashi et al., J Biol Chem, 2003), providing important implications to the therapeutic strategies of AD by γ-secretase modulation. Recently, he has established a novel method for an efficient in vitro reconstituion of γ-secretase complex, paving the way towards the structural analysis of active γ-secretase (Hayashi et al. J Biol Chem, 2004), and using thus highly purified γ-secretase particles, they have partially unveiled the submolecular structure of this complex by single-particle EM analysis (Ogura et al. BBRC, 2006). Very recently, his group has established an elegant strategy to analyze the structure-function relationship within the catalytic structure of γ-secretase complex by cystein chemistry, and demonstrated that γ-secretase harbors a water-permeable catalytic pore (Sato et al. J Neurosci, 2006), and that substrate proteins enter the catalytic pore through the lateral gate located at the C terminal side of PS (Sato et al. J Neurosci, 2008). Thus, Dr. Iwatsubo's group started from an elegant immuno-histochemical analysis of Aβ deposits in AD brains and extended it to a contemporary molecular/cellular biology of PS, that proved to play a key role in "intramembrane proteolysis".

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

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

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

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

β-sheet-rich amyloid deposits, underscoring the pathobiological role of CLAC in amyloid formation, and that CLAC inhibits fibrillization of Aβ in vitro. Knockout mice studies have confirmed the role of CLAC in neuromuscular development (Tanaka et al. J Neurosci, 2014).

4. 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.

## References


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# Department of Neurochemistry

**Professor and Head**

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**Assistant Professor**

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## Introduction and Organization

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

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

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

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

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

Following the retirement of Professor Tatsuya Haga (who became the President of Life Sciences Institute at the Faculty of Science at Gakushuin Univiersity) in March 2001, and the departure of Associate Professor David Saffen to initially University of Minnesota and then to Ohio State University in August 2001, Associate Professor Haruhiko Bito was appointed as Head of Department since January 2003. The Department is located on the 6$^{th}$ floor, in the West wing of the third building of the Medical School. The Department currently enrolls one professor, four assistant professors, four postdoctoral scholars, one technical staff member, three Ph.D. graduate students, three rotating medical students, three technical

assistants and one administrative assistant.

## 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. Nature Methods, 2013). In addition to the transcriptional regulation, we are currently investigating about the physiological function and its molecular mechanism of Arc, which is thought to be a key player that contributes activity dependent neuronal plasticity at post synaptic sites (Okuno et al. Cell 2012).

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

How do these multiple $Ca^{2+}$-dependent signaling molecules process each pattern of intracellular $Ca^{2+}$ dynamics to induce a cellular response? Recently, we have developed a method named dFOMA (dual FRET imaging with optical manipulation) to simultaneously measure activities of two distinct signaling molecules in living neurons. Applying originally developed FRET probes to dFOMA method enabled us to

measure activities of CaMKII, calcineurin and $Ca^{2+}$, when a neuron received various frequencies of synaptic inputs. These experiments provided evidence that CaMKIIα and calcineurin are fine-tuned to unique bandwidths and compute input variables in an asymmetric manner (Fujii et al., Cell Reports 2013).

In line with the visualization of neuronal activity and $Ca^{2+}$ signaling, we have developed R-CaMP2, a red genetically-encoded $Ca^{2+}$ indicator that has single-action-potential sensitivity based on rational design that takes advantage of our long-standing effort and knowledge about CaMKK-CaMKIV signaling (Inoue et al., 2015). By combining R-CaMP2 with green $Ca^{2+}$ indicator G-CaMP, distinct activity patterns between excitatory and inhibitory neurons in somatosensory cortex was revealed (Inoue et al., 2015).

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

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

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

We (and others) used GFP-actin imaging to try to understand how neuronal actin cytoskeleton in hippocampal neurons was organized and reorganized by exposure to synaptic activity. In our dissociated culture system, virtually all spines contained a high amount of GFP-actin and most of them with few exceptions were apposed to FM4-64-positive active presynaptic termini. In these cultures, increases in synaptic glutamatergic transmission by repeated bursts of high-frequency synaptic activity clearly induced several distinct kinds of activity-dependent actin mobilization, including a slow but sustained synaptic delivery of GFP-actin in a non-negligible number of activated spines and a massive but transient enhancement in cortical actin at the somatic periphery. The former was entirely dependent on NMDA-dependent $Ca^{2+}$-influx while the latter was likely to be mediated at least in part by L-type voltage-gated $Ca^{2+}$ channel activity. Thus, distinct patterns and sources of $Ca^{2+}$ influx were likely to trigger a complex spatially segregated patterns of actin cytoskeletal reorganization, with variable impact on either neuronal morphology and/or synaptic protein assembly (Furuyashiki et al., PNAS, 2002).

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

What are the key signaling pathways controlling actin dynamics in central neurons? We were especially keen to resolve the contribution of the small GTPase Rho and its downstream effectors, initially in the context of developmentally regulated neuronal morphogenesis. We first established in a model cell line N1E-115 that neurite retraction was directly linked to Rho/ROCK activity (Hirose et al., J. Cell Biol., 1998). We subsequently revealed that in central neurons, in addition to its essential role in regulating growth cone motility, Rho/ROCK activity in fact acted as a negative gate that tightly controls the timing with which the first processes are initiated out from the round cell soma (Bito et al., Neuron, 2000). Disruption of Rho/ROCK activity was sufficient to

immediately initiate neuritogenesis. This indicated that endogenous Rho activators, by titrating ROCK activity, continuously antagonized process/ branch formation and that local gradient of Rho activators might play a crucial role in shaping the timing and the extent of process formation (Bito, J. Biochem., 2003). Consistent with this idea, we found that in cerebellar granule cells, a chemokine SDF-1α released from the pia mater was likely to be a predominant Rho activator via stimulation of a cognate and specific GPCR CXCR4 (Arakawa et al., J. Cell Biol., 2003). While a true gradient in SDF-1α still remains to be demonstrated in vivo, it is intriguing to note that most active axonal process formation and elongation actually occur in the inner zone of EGL that is opposite and most distant from the interface with the pia mater (Bito, J. Biochem., 2003). Most strikingly, we demonstrated that axon elongation could actively occur in an intermediate Rho activity range that enables ROCK to be weakened enough while allowing another Rho effector mDia1 to actively mediate its effect on actin nucleation and polymerization (Arakawa et al., J. Cell Biol., 2003).

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

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

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

## Publications by lab members (January 2016- December 2016)


1. Gaffield MA, Amat SB, Bito H, Christie JM. (2016) Chronic imaging of Purkinje cell calcium activity in awake behaving mice. J Neurophysiol. 115: 413-22. (DOI: 10.1152/jn.00834.2015.)
2. Horigane S, Ageta-Ishihara N, Kamijo S, Fujii H, Okamura M, Kinoshita M, Takemoto-Kimura S, Bito H (2016) Facilitation of axon outgrowth via a Wnt5a-CaMKK-CaMKIα pathway during neuronal polarization. Mol Brain. 9:8. (DOI: 10.1186/s13041-016-0189-3.)
3. Kim CK, Yang SJ, Pichamoorthy N, Young NP, Kauvar I, Jennings JH, Lerner TN, Berndt A, Lee SY, Ramakrishnan C, Davidson TJ, Inoue M, Bito H, Deisseroth K. (2016) Simultaneous fast measurement of circuit dynamics at multiple sites across the mammalian brain. Nat Methods. 13:325-8. (DOI: 10.1038/nmeth.3770.)

# Department of Neurobiology

**Professor**

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## Introduction and Organization

The forerunner of Department of Neurobiology is Department of psychology in Institute of Brain Research, Faculty of Medicine, University of Tokyo. Department of psychology was changed to Department of Neurobiology in 1984. In 2008, Dr. Kenzo Hirose from Department of Cell Physiology in Nagoya University was appointed as a new professor.

## Teaching activities

We accept Free-Quarter students. Students are expected to experience various experimental techniques including basic fluorescence imaging techniques in living cells as well as cutting-edge technologies developed in our lab, based on their interests. For the training of Master and Ph.D. course graduated school students, we have a monthly progress report for discussing current research activities by each member who summarizes his/her recent experimental data. Further, we have a seminar by domestic and foreign guest researchers to extend our knowledge.

## Research activities

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

1) Development of novel strategy for visualizing neurotransmitters

Imaging techniques which visualize neurotransmitters in living neuronal cells are powerful method to understand the mechanism underling 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 indicators showing large fluorescence changes upon glutamate binding. This result indicates that our screening system should be applicable to develop the fluorescent indicator for other signaling molecules as well as for 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 exocytosis process is indispensable. Aiming at imaging neurotransmitter glutamate, we developed a novel optical glutamate probe by our high-throughput screening system. By using this probe, we successfully visualized pre-synaptically released glutamate following presynaptic firing with a single synapse resolution. These results indicate that our glutamate probe is useful to study presynaptic modulation and plasticity. To clarify the dynamics of exocytosis in an excitatory synapse, we tried to quantitatively analyze released glutamate at individual synapses. Our results suggest that single hippocampal synapses contain several release units.

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

Recently, nanoscale molecular distribution in synapse is suggested to be a key determinant of synaptic function. To reveal the relationship between the nano-scale molecular assemblies and synaptic functions, we are trying to perform a supereresolution microscopic analysis and imaging of synaptically released glutamate. 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.

## References

# Neuroscience

## 2. Integrative Medical Neuroscience

# Department of Child Neuropsychiatry

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**Assistant 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 2016, 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 arranged.

## 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 2016 are as follows:

- 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 pharmacotherapy and parent training for ADHD
- Effectiveness study of early intervention for autistic preschoolers and group cognitive behavior therapy for adults with high-functioning ASD

## References


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# Neuroscience

## 3. Clinical Neuroscience

# Department of Neuropsychiatry

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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, 4 clinical psychologists and 2 psychiatric social workers. In 2016, approximately 800 new patients visited our outpatient clinic, and the total visits per day was about 150.

In our inpatient wards, the secluded ward has 26 beds including 3 seclusion rooms, as well as 28 beds for the open general ward. Approximately 500 patients with various psychiatric disorders were admitted in 2016. 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 electro-convulsive 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. We also have Japan's first child psychiatry day care unit in national university hospitals since 1967, and mainly patients with pervasive developmental disorders are engaged in clinical and educational activities.

## 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 12 neuropsychiatry Ph.D. students are studying.

## Research

Our mission in research is to clarify the patho-physiology 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 and Ichiro Kanazawa. 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 Neuro-

pathology, 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 field of molecular genetics, we have developed Medical Genome 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 hereditary amyotrophic lateral sclerosis, hereditary spastic paraplegia, hereditary spinocerebellar atrophy, and hereditary multiple system atrophy. 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 preclinical study using iPSC-derived cells, searching for peripheral biomarkers in patients, and in the process of setting up a patient registry as well as an investigator-initiated clinical trial using coenzyme Q10 for patients with multiple system atrophy. Collaborative researches have achieved multiple accomplishments including identification of the causative gene for autosomal recessive Charcot-Marie-Tooth disease (*MME*), familial amyotrophic lateral sclerosis (*CCNF*), and progressive neurodegenerative encephalopathy with atypical infantile spinal muscular atrophy (*TBCD*), development of a reference database of genetic variations in the Japanese population, and case reports of SPG8 and tubular aggregate myopathy. Application of next generation sequencers for molecular diagnosis for various diseases has been intensively investigated. (Tsuji, S., Date, H., Suzuki, K., Mitsui, J., Ishiura, H., Matsukawa, T., Sato, N., Yasuda, T., Naruse, H., Matsukawa, M., Kanda, J.)

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., Terada, S., , Tokushige, S., Sasaki, T., Togashi, N., Kodama, S., Sugiyama., Y., Sato, K., Otsuka, J., Goto, R., Irie, K., and Yamazaki, A)

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.,

Ikenaga C., Uchio N., Taira K., Unuma, A).

Biochemistry lab is currently working on neuro-epigenetics using post-mortem brains of Alzheimer's disease (AD), Lewy body disease, multiple system atrophy and amyotrophic lateral sclerosis, which revealed a novel pathomechanism in AD. Based on the methylome analysis, we are on the process of verifying the pathomechanism using *in vitro* AD model of human neural progenitor cell. We are also analyzing the histone modification through neuron-specific ChIP-seq assay, which is one of the major transcriptional regulators. We also work on molecular pathology of chronic ischemia using mouse models. Other activities include development of new imaging techniques using Raman microspectroscopy. Recently we visualized spatial distribution of chemical shifts within Aβ aggregates formed *in vitro*. We also observed globotriaosylceramide distribution within peripheral nerve of Fabry's disease patient in non-labeled manner. We also developed a new optical sensor device detecting biomarkers for Alzheimer's disease using nanoimprint lithography (NIL)-based two-dimensional photonic crystal (2D-PhC). In a pilot study quantifying Aβ in CSF and serum samples, our sensor achieved higher sensitivity than conventional ELISA. Clinical study includes preclinical sporadic Alzheimer's disease cohort (AMED Preclinical study) and familial Alzheimer's disease (DIAN-J) and clinical trial of florbetapir. (Iwata, A., Nagashima, Y., Miyagawa, T., Ohtomo, R., Mano, T., Bannai, T., Tsuchida, T., Hamada, K., Mano, K, Ohtomo, G.)

Higher brain function section aims to elucidate pathophysiology and neural basis of the higher brain dysfunction in neurological disorders by means of two approaches: neuropsychological analysis of individual cases and multimodal big-data analysis. (Hayashi, T.).

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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 15 staff neurosurgeons, who participate in the three major academic activities: patient care, research, and education. The staffs include a professor/chairman, an associate professor, four lecturers and eight 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 2016 to March 2017, 18,311 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 2016, 996 patients were admitted to the neurosurgery ward. 516 surgical procedures and 90 gamma knife procedures were performed in 2016. Our practice covers a wide variety of neurosurgical diseases including malignant and benign brain tumors, hemorrhagic and thrombo-embolic cerebrovascular diseases, spinal disorders,

epilepsy, pain and movement disorders.

Intraoperative functional monitoring in brain tumor surgery and pre- and intra-operative functional mapping in epilepsy surgery are frequently used to preserve brain function as much as possible. State-of-the-art techniques including intraoperative computer-aided navigation and intravascular procedures help our continuous effort to increase the safety of surgical treatment.

Our department is affiliated with 34 neurosurgical institutions in and around the city of Tokyo including 5 university medical centers, where our residents and students are exposed to various clinical experiences. Surgical case volume in all hospitals exceeds 11,000 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, and 16 in 2017 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) Development of new therapeutic modalities for malignant brain tumors

Genotyping is now widely accepted as an essential component of pathological diagnosis in glioma. We have been routinely analysisng surgically resected tumor specimens in a semi-prospective fashion. The genetic analyses includes sequencing of IDH1/2, 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 comprehesive genetic and epigenetic approches 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.

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

We have been promoting the research on development, evaluation and standardization of the novel treatment for intractable epilepsy. Since our facility was the first in Japan to provide vagus nerve stimulation therapy, we evaluated its efficacy and safety in epilepsy treatment. We established a new intraoperative monitoring method of vagus-nerve evoked potential. Efficacy evaluation and development of surgical instruments were promoted for novel function-preserving techniques, multiple subpial transection and multiple hippocampal transection. Basic and clinical research on gamma knife treatment of epilepsy has been performed as well. For the purpose of more precise localization of epileptic foci and elucidation of epileptogenesis, we are now developing novel types of intracranial eletrodes.

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

We have been studying human brain function using not only non-invasive techniques such as fMRI, MEG, NIRS but also electrocorticography (ECoG) obtained by intracranial electrodes implanted in epilepsy patients. The latter is our markedly advantageous feature that enables us to extract brain information with much higher spatial resolution and SN ratio. We aim to understand brain mechanisms as complicated network systems and to improve the reliability of non-invasive techniques. Since ECoG is a strong candidate for a decoding source of brain-computer interface (BCI), we are planning to expand the research on this field to clinical implementation of BCI for communication and motor control in cooperation with other brain research laboratories and engineering laboratories.

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

Our department intensively utilizes various kinds of functional and metabolic imaging modalities including magnetoencephalography, functional MRI, and diffusion tensor imaging-based tractography for presurgical brain mapping. Combining the results of the 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.

6) Gamma knife radiosurgery

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

gamma knife radiosurgery in the future.

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# Social Medicine

## 1. Occupational, Environmental and Preventive Medicine

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## Introduction and Organization

The Department of Molecular Preventive Medicine was originally established in 1885. It was designed to offer both a high level of hygienic education and facilities for specialized research. At present, it is our responsibility to give lectures, seminars and courses for experiments and practical training on the preventive medicine to the third grade medical students. The professor, several invited lecturers (including adjunct staff), and research associates take part in the education as well as research activities. There are over twenty members in our department, including research fellows, graduate and under-graduate students, and guest researchers.

## Teaching activities

The field of our department covers the wide area of preventive medicine. The main scope of our education includes molecular mechanism of host defense responses to inciting environmental stimuli, free radical chemistry, and the environmental medicine with special reference to the relation between health and environment. The education is provided for the third grade medical students. The course is consisted of lectures, seminars, experiments, and practical training which are provided by our own staffs and also by the experts outside: National Institute of Infectious Diseases (Dr. Oishi), Kanazawa University (Dr. Matsugo), Kyoto University (Dr. Koizumi), Health Service Center of The University of Tokyo (Dr. Okubo), Toyama Medical and Pharmaceutical University (Dr. Inadera), Kyoto Prefectural University of Medicine (Dr. Sakai), Shinshu University (Dr. Fukushima).

## Research activities

We focus on several research fields as follows;

1) Molecular and cellular bases of chronic inflammation associated-organ fibrosis.
2) Role of cancer associated fibroblasts in tumor development.
3) Elucidation of the cellular and molecular mechanisms that lead to Graft-Versus-Host Disease.
4) Molecular analysis of chemokine receptor signaling pathway and development of novel therapeutic drugs against cancer and inflammatory diseases.
5) Application of humanized anti-CD4 antibody for cancer.

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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 2016, the Department consists of four faculty members above listed, one project lecturer (part-time), one project researcher (part-time), 2 supporting staff, 17 graduate students (15 in PhD program and 1 temporary supervised, 1 in MPH program), 18 part-time lecturers, and 27 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 medicine, 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 Department of Molecular Preventive Medicine and the other departments related to public health fields. Averagely four to five students (small group) are assigned to one special topic group with a tutor (faculty member or part-time lecturer). Each group conducts field practice, review work, or laboratory work, and writes a report in the style of original or review paper. 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 (about 35 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). 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, 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 includes, (1) evaluation of disaster preparedness in local communities and healthcare 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

# Department of Forensic Medicine

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**Lecturer**

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**Assistant Professor**

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## Introduction and Organization

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

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

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

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

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

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

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

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

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

## Postmortem examination

The determination of precise cause of death is one of the most important practices at our department. We perform medico-legal autopsies for around 120 criminal cases in eastern part of Tokyo every year. We also perform post-mortem CT at the request of police.

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

## Education

As for under-graduate education, our department provides lectures for the 4th year medical students, Free Quarter training course for the 3-4th year medical students, and Clinical Clerkship learning for the 5th 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 Clinical Clerkship learning, each student experiences the process from autopsy to presentation of expert opinion.

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

## Research

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

*1. Forensic Pathology*

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

*2. Clinical Forensic Medicine*

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

*3. Forensic Toxicology*

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

*4. Forensic Odontology*

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

*5. Forensic Genetics*

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

*6. Forensic Radiology*

Using 3D-CT, we develop new methods to perform stature and sex estimation using the measurements of various bones. We investigate the merit and demerit of post-mortem imaging to determine the cause of death.

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# Department of Biomedical Informatics

**Professor**

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**Assistant Professor**

Katsuya Tanaka, Ph.D.

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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

Teaching staffs are Professor Kazuhiko Ohe, Associate Professor Takeshi Imai, Assistant Professor Katsuya Tanaka, Hidenao Atarashi, Yoshimasa Kawazoe, Research Associate Shinichiro Yokota and Daisuke Sato.

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 Shool of Public Health: We offer 2-year Master of Publics Health (M.P.H) course and the 1-year M.P.H program in the School of Publics Health. See the homepage of the School of Publics 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 FY2016 are five 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) analysis of localization and restructuring of medical human resources.

In these domains, major research topics are as listed below.

1) A study on development of large scale ontology databases of medical terms and concepts and development of application systems using the ontology: This research is to develop a methods to build a large scale medical ontology, which is a database for hundreds of thousand of clinical terms and concepts and their relationships. The medical ontology covers over 6000 diseases and whole of human anatomical structures using HOZO ontology describing tool, and the ontology was converted from the HOZO-proprietary XML data format into the LOD format. Using the LOD format, a web application for browsing the disease ontology was developed and published on the web site; http://lodc.med-ontology.jp/

2) Development of Multi-purpose Clinical Data

Repository System(MCDRS) and Joining the University of Tokyo COI (Center of Innovation ) Project named “Self Management of Your Health”: The department joined “Clinical Outcome Database Project” sponsored by MHLW in 2014 and developed MCDRS as a system for registration of clinical case data by clinical researchers. The system is now under public release for other database projects.

On the other hand, 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 vender-proprietary database format into the international standard format and facilitating easy multi-purpose secondary use for clinical researches and other researches in social medicine area.

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

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# Internal Medicine

## 1. Medicine Ⅰ

# Department of Cardiovascular Medicine

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## Introduction and Organization

The Department of Cardiovascular Medicine was established in 1998 by regrouping cardiologists of five previous internal medical departments. After Yoshio Yazaki, the first professor, and Ryozo Nagai, the second professor, the present professor Issei Komuro was elected in August, 2012. Our department comprises one professor, 4 lecturers, 2 hospital lecturers, 15 research assistants, 11 staff members, and 46 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 2016, a total of 1,926 patients were newly admitted to our hospital ward of 60 beds. The average duration of hospitalization was 12.2 days.

Because we are an authorized facility for heart transplantation, the use of left ventricular assist device in cases of severe heart failure has been increasing. In 2006, the first patient with heart failure from our department underwent a heart transplant procedure at the Department of Cardiovascular Surgery. In 2016, 12 patients underwent heart transplant (total 78 cases). In March 2014, our facility was also authorized to perform lung transplantation. Cardiovascular angiography was performed in 1,647 patients, of which 523 patients underwent interventional procedures. CT coronary angiography and cardiovascular MRI were performed in 409 and 76 patients, respectively. With regard to arrhythmias, there were 331 cases of catheter ablation, 68 cases of implantation or replacement of pacemakers and other specialized pacemaker devices, including 19 cases of implantation or replacement of implantable cardioverter-defibrillator and 10 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 208.3 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, and Marfan's syndrome. 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. Investigation of disease pathophysiology and development of novel therapies (severe heart failure, cardiac transplantation, congenital heart disease, etc.)
7. New treatments for structural heart disease
8. Diagnosis and treatment of Marfan's syndrome and adult congenital heart disease
9. New treatments for pulmonary hypertension
10. New treatments for congenital heart disease
11. Aerobic threshold and cardiac rehabilitation
12. Imaging techniques (echocardiography, MRI, CT, and SPECT) in cardiovascular diseases

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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 associates. In the University of Tokyo, affiliated hospitals and foreign institutions, approximately 60 members belong to the Department. In the University of Tokyo Hospital, about 23 respiratory physicians are doing clinical works.

Based on the fact that the number of patients with respiratory diseases such as primary lung cancer and COPD is tremendously increasing, advancement and fruitful results of researches on respiratory medicine are more and more expected. In this era, we are conducting basic and clinical researches for wide variety of respiratory disorders including primary lung cancer, COPD, asthma and interstitial lung diseases. Especially, we have been intensively studying the 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 the out-patient care as well as care of in-patients (35 cases on average), which is taken at the 13$^{th}$ floor of the hospital ward A of the University of Tokyo Hospital. Our practice is performed by the three-member system of a junior resident, a senior resident and an experienced associate.

Main diseases of in-patients are primary lung cancer, respiratory infections, interstitial pneumonia, and COPD. Many patients with primary lung cancer also have interstitial pneumonia or COPD as their back ground pulmonary diseases. There are many emergency visits and admissions with pneumonia, respiratory failure due to exacerbation of COPD or interstitial pneumonia, progression of lung cancer, and so on. In cases of severe respiratory failure such as severe pneumonia and ARDS, we conduct ventilatory support of such patients in collaboration with ICU staff in an effort to rescue them. A specialized clinical conference for respiratory disease has been held once a week since late 1990s, where staff of our department, department of thoracic surgery and department of

radiology join and discuss together to make best diagnostic and therapeutic approach to individual patients. This conference has been highly appreciated as 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 in our hospital. Our department contributes to the pre- and post-surgical evaluation of respiratory functions, and also receives consultation about respiratory complications from almost every department in our hospital

At present, there increase highlighted interests in respiratory medicine. Primary lung cancer is now leading cause of cancer death, and is one of the major medical and social problem to be overcome. Recently, the new developments and their remarkable effectiveness of molecular-targeted therapies in primary lung cancer attract much attention in the fields of both basic science and clinical practice. Respiratory infections are now the 3rd leading cause of all death and COPD also will be major leading cause of all death in the near future. Among respiratory diseases, there are several disorders to which no effective therapeutic modalities are currently available. For example, ARDS is an acute lung injury and the mortality rate for ARDS is extremely high despite of intensive care using currently available tools. Idiopathic pulmonary fibrosis is a progressive and fatal inflammatory and fibrotic disorder of the lung parenchyma, while only a few medications are currently available to treat the disease. We would like to make every effort to develop a novel and potential therapeutic approach to these diseases.

Number of in-patients in 2016

| | | |
|---|---|---|
| 1. | Primary lung cancer | 154 |
| 2. | Abnormal chest X-ray | 81 |
| 3. | Respiratory Infection | 59 |
| 4. | Interstitial pneumonia | 57 |
| 5. | Sarcoidosis | 10 |
| 6. | COPD | 6 |
| 7. | Malignancy other than primary lung cancer | 5 |

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

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

## Teaching activities

As for under-graduate education, our department takes part in systematic lectures and specific learning for diagnosis and treatment of respiratory diseases for the 4th year medical students, clinical clerkship for the 5th year medical students, and clinical lectures for the 5th and 6th year medical students. Elective clerkship for the 5th year students is actively performed in collaboration with expert respiratory physicians from several leading affiliated hospitals.

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

In clinical lectures, we present clinical cases of important diseases such as primary lung cancer and pneumothorax, and try to discuss several important points on the diagnostic evaluation and treatment in collaboration with the Faculty of the Department of Thoracic Surgery. Recent major advance in the relevant fields are also reviewed.

During the period of clinical clerkship, each student, as a member of medical care team, has opportunities to experience the daily clinical care with junior and senior residents as well as with the Faculty. Each student can learn how to make a medical interview, check physical findings and make the actual plans for the diagnosis and treatment. The respiratory specialists provide lecture on fundamental chest radiology as one of essential elements in clinical clerkship and this lecture is highly appreciated by the students.

Elective clerkship at the 5th year of the educational program is actively performed 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 a relatively long period (each for two weeks). Several lectures on the specialized

theme on respiratory diseases are also provided.
As for post-graduate education, respiratory physicians (one senior resident and one associate) assemble a team with one junior resident, and provide medical cares for patients with various respiratory diseases. Under these processes, residents are able to acquire the 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, and so on are held at regular interval.

## Research activities

Our department is conducting basic and clinical researches for various respiratory disorders including primary lung cancer, COPD, asthma, interstitial pneumonia, respiratory infections and others. Epidemiological, clinical, cellular and molecular biological 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 the Faculty members make considerable effort to study about genetic alterations in primary lung cancer, cell biological analysis using airway epithelial cells, fibroblast and smooth muscle cells, both in collaboration with the Faculty of the Department of Thoracic Surgery, analysis of genetically-engineered mice as disease-models and so on. These results have been presented and/or published in the Scientific Meeting and/or peer-review 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 primary lung cancer and their clinical applications.
Search for previously unidentified oncogenic driver mutations in lung cancer and elucidation of resistant mechanisms against molecular-targeted dugs.
Analysis of functional alterations of airway epithelial cells and fibroblasts in relation to tissue repair and remodeling, especially 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 primary lung cancer.
Epidemiological study of respiratory diseases, using Diagnosis Procedure Combination database.

Takahide Nagase is working as a GOLD National Leader.

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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, 2 lecturers, 21 associates, 12 fellows, 67 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, fourth and fifth 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 and First Research Building as in the other departments.

## Clinical Activities

The Department of Gastroenterology is in charge of about 90 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 11 days. Resident, junior and senior staff members bear the responsibility for a medical management of each inpatient, in collaboration with subspecialty groups concerned. The staff members examine about 5,700 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 2016). Number of treatments for hepatocellular carcinoma treatments, represented by percutaneous radiofrequency ablation, exceeded 400 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, ERCP is performed 1000 cases per year. The cumulative number of endoscopic papillary balloon dilation (EPBD) for treatment of bile duct stones exceeds 1,500. In addition, EST (endoscopic sphincterotomy) or EPLBD (endoscopic papillary large balloon dilation) is also applied to achieve the best outcomes for every case. 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, a numbers of advanced procedures are performed in our department: 200 balloon-assisted ERCPs for surgically altered anatomy cases, 200 EUS-FNAs and 50 EUS-guided interventions. In combination with these interventions, clinical trials of chemotherapy are conducted to improve the prognosis of pancreatobiliary cancer.

In the gastrointestinal field, ESD (endoscopic submucosal dissection) is performed as a curative endoscopic treatment for neoplasms in esophagus, stomach or colon (more than 360 patients a year). Non-exposed endoscopic wall-inversion surgery (NEWS), which was developed with the Department of Gastrointestinal Surgery, now expanded its clinical application from the resection of GIST to the treatment of gastric cancer. Double-balloon endoscopy and capsule endoscopy enabled the examination of whole small intestines (320 cases in 2016). All those interventions are performed by the members of our department, who were specially trained for each technique. In addition, for the management against inoperative malignancies, we effectively combine the interventional treatments with various chemotherapy regimens including new molecular-targeting drugs.

On outpatient basis, ultrasonography, gastroduodenal endoscopy, and colonoscopy is performed on 12,500 patients, 9,700 patients, and 6,200 patients per year respectively. In the endoscopy examinations, we diagnose about 760 cases of gastric cancer and 1300 cases of colorectal tumor annually, and about 50% 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 have the opportunity taking systematic and clinical lectures on gastroenterology from the staffs of our department. Several courses of practical teaching are also provided for the students. Particularly, in the clinical clerkship program for the fourth grade students, each student joins in the team of staff physicians and learns digestive diseases practically via the communication with the inward patients. At the end of period, the students make a summary presentation of the patient to the professor, and also outline articles from world's leading medical journals.

The residents of internal medicine participate in the training in the Department of Gastroenterology for 1-4 months in the first year. They learn the therapeutics and diagnostics in gastroenterology as well as general internal medicine. Depending on their interest in gastroenterology, they can learn advanced techniques in gastroenterology in the affiliated

hospitals for next few years. They come back to the department as a graduate student, and start medical researches either in basic or clinical research area. Currently, 67 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 molecular elucidation of carcinogenesis in gastroenterological neoplasms, metabolic aspects of viral hepatitis, mechanisms of replication of hepatitis viruses, pathogenesis of NASH, mechanisms of liver regeneration and fibrosis, pathogenesis of *Helicobacter pylori* infection, molecular characterization of gastrointestinal morphology, establishing new animal models for various diseases in our area, etc. Based on such new concepts as non-coding RNA, cancer stem, or organoid, we performed various experiments.

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, a combination therapy of gemcitabine/S-1/leucovorin for unresectable or borderline resectable pancreatic cancer, a randomized controlled trial of covered metallic stent with anti-reflux system, endoscopic treatment of walled off necrosis a large bore covered metal stent, 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

# Department of Nephrology and Endocrinology

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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, epigenetics, carbonyl stress and endoplasmic reticulum stress.
2. Investigation of causes of atypical hemolytic-uremic syndrome.
3. Roles of renal proximal tubule transport in the regulation of plasma volume and blood pressure.
4. Physiological and pathological significance of Na-$HCO_3$ cotransporter NBCe1.
5. Investigation on pathogenesis of disorders and treatments of mineral and bone metabolism
6. Molecular mechanism of G protein-coupled receptor-mediated signal transduction
7. Development of a new drug and strategy targeting G protein-coupled receptor.

## Department of Hemodialysis & Apheresis

**Introduction and Organization**

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

This new Center for Hemodialysis is equipped with one pressure control unit in addition to 12 hemodialysis machines under a state-of-the-art hemodialysis control system. Our concept of a hemodialysis controlling system is a hub to transfer all digital and analog data from patients and to monitor machines, including blood purification machines, to the host computer in our hospital, centralizing all data and administering medical coding and billing robustly. Blood purification machines in the ICU can be monitored seamlessly under the cloud system of our hospital. Blood purification machines are selected uniformly to secure patients' safety while avoiding human error and increasing the overall educational quality of staff members.

**Clinical activities**

1. Start of maintenance hemodialysis therapy for end-stage renal disease (ESRD).
2. Regular hemodialysis therapy for hospitalized ESRD patients. Please note that our center does

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

**Education**

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

**Research**

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

## Publications

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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) and Dr. Toshiro Fujita (2003) and current professor Dr. Takashi Kadowaki (2003-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 and the 4th floor of the Ward B of the University of Tokyo Hospital, and take care of 612 new inpatients per year. Besides the staffs listed above, our division holds faculties in branches, for example, Department of Clinical Nutrition Therapy (Associate Professor: Dr. Naoto Kubota), Department of Molecular Sciences on Diabetes (Project Associate Professor: Dr. Hironori Waki [since Sep 2016], and Project Assistant Professor: Dr. Masatoshi Kobayashi), Department of Integrated Molecular Science on Metabolic Diseases (Project Associate Professor: Dr. Masato Iwabu, and Project Lecturer: Dr. Miki Okada-Iwabu), Division of Biophysics, Center for Disease Biology and Integrative Medicine (Lecturer: Dr. Noriko Takahashi), Ubiquitous Health Informatics (Project Associate Professor: Dr. Kayo Waki), Clinical Epidemiology and Systems (Project Assistant Professor: Dr. Mikio Takanashi), Division for Health Service Promotion,

The University of Tokyo (Assistant Professor: Drs. Sachiko Okazaki and Tomohide Yamada), Clinical Research Support Center (Project Assistant Professor: Dr. Akiko Kishi) and Department of Clinical Laboratory (Assistant Professor: Dr. Makoto Kurano). 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 15 students of Graduate School in our division. With all these 56 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 180 patients per day (total 43,155 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 Kadowaki.

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

## Research activities

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

1) Molecular mechanisms of type 2 diabetes

We have been attempting to elucidate the mechanisms underlying the development of type 2 diabetes at the molecular and genetic levels. To this end, in

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

2) Pathophysiological roles of lipid storage and atherosclerosis

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

3) Clinical trials and epidemiological studies

We are conducting clinical trials and epidemiological studies including “Japan Diabetes Optimal Integrated Treatment study for 3 major risk factors of cardiovascular diseases (J-DOIT3)” follow-up study, "Japan Diabetes compREhensive database project based on an Advanced electronic Medical record System (J-DREAMS)", 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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## 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 one lecturer, one special lecturer (hospital), and 7 assistant professors.

## Clinical activities

On the average, 55-65 patients with hematological diseases are treated in the ward. Clinical facilities include patient rooms with high-efficiency particulate air filtration and filtrated water supply. Patients who are eligible for the treatment with high-grade infection prophylaxis are admitted to the facilities. Patient care is provided by team management. That is, three doctors (a junior resident, a senior resident, and an assistant professor) are assigned to a single patient. Since clinical issues are highly related to hematopoietic stem cell transplantation especially for patients with hematological diseases, a substantial portion of our clinical conferences are shared with staff members of the Department of Cell Therapy and Transplantation Medicine and the Department of Pediatrics (Hematology/Oncology). Many problems arising in daily clinical practice are discussed in the morning clinical conference held thrice a week. Diagnostic and therapeutic issues as well as pathological aspects of indicative and/or educational cases are discussed in clinical conferences held twice a month.

Outpatient clinical services are provided from

Monday to Friday in the morning and afternoon using three booths. Approximately 60-65 patients visit our outpatient clinic every weekday. One of our ultimate goals in the clinical activities is to cure patients with hematological malignancies.

We perform various kinds of genetic or molecular tests to detect, characterize, and monitor neoplastic cells and their results are used in the diagnosis and treatment.

Here we introduce technical aspects on the treatment strategy:

1. High dose chemotherapy with autologous stem cell transplant: High-dose chemotherapy is administered for the treatment of hematological neoplasms and solid tumors. For the autologous stem cell support, peripheral blood stem cell is usually selected as a source of stem cells.
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. Allogeneic hematopoietic stem cell transplant for the elderly are performed under the admission of the ethical committee of the Faculty of Medicine. 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, (7) regulation of hematopoiesis. 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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# Department of Allergy and Rheumatology

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The Department of Allergy and Rheumatology presently consists of 13 staffs mentioned above, who preside over 5 medical staff, 20 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 13th 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 about patients 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 has 5 research 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 cell metabolism modification by a nobel regulatory T cell subset and inhibitory cytokines.
3. Analysis of the mechanisms of tolerance breakdown to systemic autoantigens.
4. Analysis of T cell and B cell repertoires in autoimmune diseases.
5. Analysis of autoimmune susceptable gene functions in mice and human modles.
6. Analysis of signal transduction mechanisms in autoimmune diseases.
7. Analysis of autoimmune disease-specific iPS cells
8. Exploration of the roles of protein prenylation in the animal models of lung disease.
9. Analysis of bone strength in glucocorticoid-induced osteoporosis.
10. Investigation of biomarkers in autoimmune disease.

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# Department of Infectious Diseases (Internal Medicine)

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## Introduction and Organization

The Department of Infectious Diseases has been one of the leading academic organizations specialized for internal medicine, in particular, infectious disease medicine in Japan since 1998, when the Departments of Internal Medicine, established in 1890, were rearranged into new ones according to subspecialty of internal medicine. Our department has been chiefly engaged in clinical, educational and research activities for infectious diseases including bacterial, fungal and viral infections of all organs including HIV infection, tuberculosis and viral hepatitis. Our department is located on 11$^{th}$ 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, two 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 11$^{th}$ 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 under-graduate medical students according to the education-al programs of the University of Tokyo. For the fourth year medical students, six lectures of infectious diseases are given. In addition, principles of medical diagnosis are taught at the bedside. During the bed-side teaching for fifth and sixth year students, our associates teach them on man-to man basis the basic

way of thinking for correct diagnosis and therapy, the techniques of interrogation and physical examination, the way for interpretations of laboratory tests and other medical examinations, and the basic medical procedures on each case. The education of junior residents 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 two to three 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 *Clostridium 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

## Members

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# Department of Stress Science and Psychosomatic Medicine

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## Introduction and Organization

The Department of Stress Science and Psychosomatic Medicine is one of 11 divisions of the Department of Internal Medicine, the University of Tokyo. It covers eating disorder, panic disorder, and various psychosomatic diseases such as chronic headache, irritable bowel syndrome, functional dyspepsia, hypertension, diabetes mellitus, and hyperthyroidism. Our teaching staff consists of one associate professor, two associates, and 5 adjunct professors, and other members are 2 senior residents, 7 graduate students, and 2 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 2016 April to 2017 March, overall 1,802 patients (67 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 2016 April to 2017 March, the numbers of the new outpatients and of the overall outpatients in our department were 240 and 4,092, respectively.

## Teaching activities

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

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

## Research activities

Targeting stress-related diseases such as not only those covered by our department but also other lifestyle-related disease, and cancers, we are investigating their pathophysiology and psycho-

pathology through assessing bio-psycho-behavioral time-series data, various questionnaire data, and autonomic nervous function. We are also actively conducting basic as well as clinical research on eating-related substances.

Some representative research methods are as follows:

1) Ecological momentary assessment (EMA): Investigation on neurobehavioral basis of stress-related diseases such as tension-type headache, eating disorders, insomnia, and panic disorder using portable computers for real-time assessment of subjective symptoms in combination with ambulatory monitors such as electrocardiogram and actigraphy.
2) Neuroendocrinological and neuroimmunological studies in anorexia nervosa patients: multi-disciplinary investigation on energy metabolism during a refeeding phase; changes in various substances such as neuropeptides before and after treatment; relationship between bone metabolism and various makers; and exploration of biomarkers for evaluating treatment efficacy.
3) Psycho-oncology: Development of a new questionnaire for evaluating depressive mood in cancer patients.

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

# Department of Transfusion Medicine

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## Introduction and Organization

The Transfusion Medicine service was established in 1949, as an internal provisional measure, and officially established in 1966. In 1984, Professor Hiroshi Toyama assumed as the first Professor of the department. Professor Toyama greatly contributed to the field of transfusion medicine, especially by publishing "Transfusion Medicine" (actually in its 3rd. edition), which is the bible of transfusion medicine in Japan. Other great contributions from the department are as follows. Dr. Kazuo Okochi, ex-lecturer of the department, is the pioneer in the field of transfusion-associated hepatitis research, ex-Professor Takeo Juji clarified the mechanisms of transfusion-associated graft-versus-host disease (TA-GVHD), a serious post-transfusion complication, and ex-Professor Yoichi Shibata contributed enormously to the field of platelet immunology. In 1997, the Department of Transfusion Medicine was established as a chair of the Division of Internal Medicine of the Graduate School of Medical Sciences, the University of Tokyo.

Actually, the department is composed of 6 medical doctors (4 full-time, and 2 partial-time), 10 laboratory technicians, 2-3 nurses and 1 office assistant.

## Clinical activities

The main activity of the department of Transfusion Medicine is the control, preservation, and provision of safe blood products and their derivatives (including albumin). The control of all blood products in the hospital is centralized to the department, which, in addition, provides information and orientation related to blood transfusion. Transfusion-related laboratory tests and tests for transfusion-transmitted infectious diseases are routine practices of the department, which also actively takes part in the diagnosis, prevention and treatment of adverse reactions and post-transfusion complications. Collection, preservation and provision of autologous blood are also important functions of the department, where the outpatient clinic for autologous blood was established by ex-Professor Koki Takahashi in January 2006. At the outpatient clinic, the first established in Japan, the transfusionist gives consultation to the patients, prepares the adequate blood collection schedule, takes the informed consent, and performs the blood collection, according to the surgeons' needs. Additionally, collection and preservation of peripheral blood stem cells are also performed.

The main activities are as follows:

I Control and preservation of blood products and its derivatives;

II. Laboratory tests

1) Blood typing and histocompatibility testing;
2) Detection of anti-erythrocyte, anti-leukocyte and anti-platelet antibodies;
3) Detection of HBV antigens and antibodies, HCV, HAV, HTLV and HIV antibodies;
4) HLA typing for hematopoietic stem cell trans-plantation and organ transplantation;

III.Clinical work

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

## Teaching activities

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

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

## Research activities

Research on red cells, leukocytes, and platelets, the post-tranfusional complications, transplantation immunology, immunotherapy, and stem cell biology are the main themes of the department. Typing of blood cells is performed by serological and DNA-based methods. The HLA typing, which was introduced by ex-Professor Takeo Juji, one of the pioneers of this field, is an essential test for hematopoietic stem cell and organ transplantations, and still continues as one of the most important research fields of the department. The mixed-passive hemagglutination (MPHA) method, the most popular methodology for platelet serology in Japan, was developed by ex-Professor Yoichi Shibata and its applicability is now extended for granulocyte as well as endothelial cell serology. Transplantation immunology, including stem cell biology is also an important subject. Also, development of new materials for medical use is also being researched. Recently, the risk factors of the detrimental effects of autologous blood donation, especially focusing on the noninvasive measurement of circulating blood volume, are being investigated. Following are the main themes.

1. Detection of platelet alloantigens and antibodies and their role in the transfusion practice.
2. Diagnosis and prevention of post-transfusional complications and thrombocytopenic purpura of the newborn.
3. Clinical application of refrigerated and frozen-stored blood for autologous transfusion in surgical patients, and the improvement of the preservation methods.
4. Study on the effect of pre-storage leukoreduction of autologous blood for the prevention of possible adverse effects.
5. Development of a new methodology for platelet cross-match.
6. HLA and HPA genotyping.
7. Development of a new methodology for evaluation of platelet function.
8. Ex-vivo expansion of hematopoietic stem cells and their clinical application.
9. Pathophysiology of TRALI and TACO.
10. Study on the risk factors of autologous blood donation.
11. Development of new materials for medical use.

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# Reproductive, Developmental and Aging Sciences

## 1. Obstetrics and Gynecology

# Department of Reproductive Endocrinology

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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 4) effect of ovarian steroid hormones on bone metabolism, and 5) effects of endocrine disrupters on the reproductive system.

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# Department of Gynecologic Oncology

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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 both clinical and research activities, as well as teaching activities, with 19 associates of the University of Tokyo Hospital. For the clinical aspect, they are engaged with in-patient and out-patient care.

## Activities

**(1) Oncology research**

In our division, the pathogenesis of cervical cancer, endometrial cancer, and ovarian cancer have been investigated these two decades.

Cervical cancer is associated with a subset of high-risk HPVs. The most prevalent of these, types 16 and 18, together account for more than 70% of cases. HPV infections are very common among young sexually active women, and the majority of infections are transient and cleared by their immune system within a short period, with 70% of infections deleted in 1 year and 90% in 2 years.

Studies of virus neutralization by antibody are prerequisite for development of a prophylactic vaccine strategy against HPVs. To determine whether neutralizing anti-bodies (NAs) against HPV16 is responsible for a higher regression rate of low-grade cervical intraepithelial neoplasia (CIN1), we investigated an association between the presence of the NAs and the fate of the HPV16-related CIN1. The incidence of the presence of the NAs in the women with a non-pathological cervix (85.7%) was significantly higher than in the CIN1 cases (21.5%), the CIN2/3 cases (15.7%), and the cervical cancer cases (0%) ($p<0.0001$). The regression of the CIN1 lesion was closely associated with the presence of the NAs ($p=0.0002$). The presence of the NAs was associated with low-level copy number of the viral DNA relative to the NA-negative group ($p=0.05$). The presence of the NAs against HPV16 was associated with a higher regression rate of HPV-related CIN1 lesions. The NAs seem to have a role in deterring HPV-related cervical lesions from progressing to CIN2/3 by inhibiting the infection with de novo replicated HPV. Then we designed a placebo-controlled trial in healthy adults to evaluate the safety and immunogenicity of a synthetic peptide consisting of the aa 108-120 of HPV16 L2 (L2-108/120) region, because this region contains a cross-neutralization epitope against genital HPV.. A total of 13 volunteers were given nasal inoculations with 0.1 (n=5) or 0.5mg (n=5) doses of the peptides or placebo (n=3) without adjuvant at weeks 0, 4, and 12. Sera were collected before inoculation and at 6, 16 and 36 weeks. The inoculation caused no serious local and systemic complications. The inoculation generated anti-L2 antibodies binding to both HPV16 and 52 L1/L2-capsids in four of the five recipients in the

0.5mg group. Sera of the four recipients showed neutralizing activities against HPV16 and 52. Serological responses to the peptides were not found in the 0.1mg group and the placebo group recipients. This study suggests the L2-108/120 peptide is tolerable in humans and has the potential as a broad-spectrum prophylactic vaccine against genital HPV.

In endometrial cancer, we identified novel mutations in *PIK3CA* and *AKT1*, and reported that inhibiting the Phosphatidylinositol 3-kinase (PI3K) / Akt pathway showed anti-tumor effect in endometrial cancer cells. We have identified other candidate molecular targets in endometrial cancer. For example, high expression of survivin, an anti-apoptotic protein, is associated with poor prognosis. We found that survivin inhibitor, YM155, dose-dependently and significantly increased the apoptotic cell population in all endometrial cancer cell lines examined. In addition, we elucidated that the histone methyltransferase EZH2, a key epigenetic modifier, is significantly over-expressed in endometrial cancers, and that EZH2 inhibitor suppressed endometrial cancer cell growth. We also investigated molecular biomarkers to predict the prognosis and/or drug sensitivity in endometrial cancer, using genome-wide analyses in clinical samples. Of note, extensive chromosomal instability was an independent poor prognostic factor in endometrial cancer.

In ovarian cancer, we also investigated genome-wide analyses, including whole-exome sequencing and gene expression array, in high-grade serous and clear cell carcinomas. As well, we examined various types of molecular-targeted drugs in ovarian cancer cell lines. For example, we identified a subgroup in ovarian clear cell carcinomas, which is associated with prognosis and chemosensitivity. We reported several molecular targets in ovarian clear cell carcinomas. Targeting the PI3K pathway showed anti-tumor effect through induction of wild-type TP53. We further identified that MDM2, a negative regulator of TP53, is frequently overexpressed and that MDM2 inhibitor induced TP53-mediated apoptosis in ovarian clear cell carcinomas.

**(2) Clinical oncology**

In our department, more than 150 patients with gynecological cancer are treated every year. And also, we play an important role in clinical trials of JCOG (Japan Clinical Oncology Group) and JGOG (Japanese Gynecologic Oncology Group). For example, we conducted a non-randomized confirmatory phase III trial (JCOG1101) in Japan to evaluate the efficacy of modified radical hysterectomy in patients with tumor diameter 2 cm or less FIGO Stage IB1 uterine cervical cancer, for which the current standard is radical hysterectomy. This study began in January 2013 and a total of 240 patients will be accrued from 44 institutions within 5 years. The primary endpoint is 5-year survival. The secondary endpoints are overall survival, relapse-free survival, local relapse-free survival, percent completion of modified radical hysterectomy, percent local relapse, percent pathological parametrial involvement, days until self-urination and residual urine disappearance, blood loss, operation time, percent post-operative radiation therapy, adverse events and severe adverse events.

In addition, we have performed a lot of single-institution analyses in clinical setting. For example, to evaluate the efficacy and toxicity of systematic lymphadenectomy and postoperative radiotherapy (PORT) in the treatment of endometrial cancer (EC), a total of 256 patients with EC between 2000 and 2008 were retrospectively analyzed. Surgery included systematic pelvic and aortic lymphadenectomy, whereas pelvic lymphadenectomy alone was performed to preoperative stage I patients with superficial myometrial invasion and G1 endometrioid adenocarcinoma. PORT was administered to 67 patients with positive lymph nodes, deep myometrial invasion, or adnexal/peritoneal metastases. Prior to PORT, 37 patients with adnexal/peritoneal involvement or aortic node metastases were treated with chemotherapy. Surgery was undergone in 247 patients, including with 215 pelvic lymphadenectomy and 126 aortic lymphadenectomy. Five-year survival was 97.0% for stage I, 83.3% for stage II, 84.1% for stage III, and 45.2% for stage IV. In PORT group, 13 (19%) were recurred including one (1.5%) intrapelvic recurrence, and five-year survival was 96.7% for intermediate-risk group and 85.3% for high-risk group. Among the

patients who had received lymphadenectomy, 19 (8.8%) experienced severe (more than grade 3) ileus and 18 (8.4%) developed severe lymphocystitis. The frequency of severe ileus in PORT group was significantly higher than that in non-PORT group (14/65 vs. 5/150, P<0.0001). The rates of adverse effects were irrespective of aortic lymphadenectomy. This study suggested that surgery with systematic lymphadenectomy followed by PORT was associated with good prognosis but increased rates of ileus in patients with EC. PORT subsequent to lymphadenectomy should limit to relatively high-risk patients.

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# Department of Perinatal Medicine

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## Organization

The Department of Perinatal Medicine is organized by one professor and one associate professor, being directed practically by Professor Tomoyuki Fujii, the chairman of the Department of Obstetrics and Gynecology. All the staff members are taking part in both the clinical and research activities, as well as the teaching activities, with 19 associates of the University of Tokyo Hospital. For the clinical aspect, they are engaged with in-patient and out-patient care including the activities in the delivery units.

## Activities

The 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]

By the advance of the techniques for prenatal diagnosis of fetal growth and congenital malformations, the area of fetal medicine is enlarging. Strict measurement of fetal growth during pregnancy has made possible the accurate diagnosis of fetal growth restriction. New techniques like fetal blood sampling and three-dimensional ultrasonography have been introduced into clinical service. The perinatologists and medical engineering team in our department are working on clinical research to clarify the patho-etiology of preterm birth and preeclampsia. Perineal ultrasound is a new approach for assessing labor progress. Using this technique, we are challenging to establish objective evaluation of labor progress which can contribute to safer labor management.

Recurrent pregnancy loss (RPL) is a condition when a woman has two or more clinical pregnancy losses. Our “special clinic for RPL” opens once a week. About 200 new couples with RPL visit us in a year. The patients are checked several risk factors of RPL, such as anatomical, chromosomal, hormonal, biological, or autoimmune factors. To RPL women with autoimmune factors, especially with anti-phospholipid antibodies, anti-coagulation therapy is performed. For low risk group, low dose aspirin is administered. Heparin injection is performed for high risk group, for instance, patients with successive intrauterine fetal death during the second or third trimester of pregnancy, or those with beta-2 glycoprotein I dependent anticardiolipin antibody. Causative factor is not detectable in a 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 of their mental status with the outcome in the subsequent pregnancy.

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## Organization

The Department of Molecular and Cellular Reproductive Medicine is organized by one professor and one associate professor.

## Activities

Our department mainly aims to investigate the reproductive functions, and molecular biological methods are utilized to accomplish this purpose. Basic researches are currently performed and we are revealing many interesting findings annualy. We specifically focus on the role of inflammation and transcription machinery in these issues.

1) The mechanism of folliculogenesis, follicular atresia and intrafollicular microenvironment in the ovary.
2) The physiological functions of sex steroid hormones and gonadotoropins.
3) The molecular mechanisms of endometriosis.
4) The molecular mechanisms of uterine fibroid and adenomyosis.
5) The effects of aging 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 400 cases annually.

In accordance with the notion of life stage specific approches, we also manage patients complaining primary/secondary amenorrhea, infertility, dysmenorrhea, heavy menstrual bleeding, and climactirium. Osteoporosis in relatively younger generation might be a heavy burden for patinets and we have already established the primary care system for these women.

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# Reproductive, Developmental and Aging Sciences

## 2. Pediatric Sciences

# Department of Pediatrics, Department of Developmental Pediatrics

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(As of March 31, 2017)

**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 1 professor, 3 associate professors, 5 lecturers, 18 associate professors, 14 senior residents, 2 research fellow, and graduate students on March 31, 2014.

The outpatient clinic of our department is located on the second floor of the outpatient clinic building. The inpatient ward and conference rooms are located on the second floor of the inpatient clinic building A. Offices are on the second and third floors of the East Research Building. Our laboratories are located on the second, third and fourth floors of the Research Building of Internal Medicine and on the second and third floors of the East Research Building.

## Clinical activities

We have specialized outpatient clinics covering all pediatric fields in addition to general pediatrics. In July, 2008, the capacity of the pediatric and pediatric surgery ward was increased to 100 beds, including 9 beds in the neonatal intensive care unit (NICU), 15 beds in the growing care unit (GCU) and 6 beds in the pediatric intensive care unit (PICU), and our institution is going to fulfill the designation as children's hospital affiliated to the university hospital. In NICU, we are taking care of small premature babies weighing from 400g to 4,000g often associated with congenital disorders requiring invasive interventions. A 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 glomeluro-nephritis, purpura nephritis and renal and/or urinary tract anomalies), endocrinological disorders, metabolic disorders and psychosomatic diseases are admitted in the wards. Approximately 10 patients received hematopoietic stem cell transplantation every year. There are patients with severe combined immuno-deficiency, aplastic anemia-myelodysplastic syndrome, relapse/refractory acute lymphoblastic leukemia, acute myeloid leukemia and high-risk neuroblastoma.

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 the patients and help their mothers, providing enormous comfort to both the patients and their mothers. Various activities are scheduled for the patients in the hospital such as the 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 and pediatric diagnosis for 36 hours to the second year students, and clinical bedside learning in the inpatient ward for 2 weeks to the third year students. During bedside learning for 2 weeks, specialized teaching sessions, like seminars are held every day. In the outpatient learning, medical students take histories and perform physical examinations of patients under the supervision of the teaching staff. On the second and third days of the outpatient clinic, each student visits the local pediatricians or local hospitals in and around Tokyo. On the last day of clinical learning, the Professor and an Associate Professor evaluate the students' achievements. We have an elective clinical clerkship course for the third year 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.

① Hematology/Oncology group: To explore molecular mechanisms of pediatric malignancies, we performed target capture sequencing, whole transcriptome sequencing and genome-wide methylation analysis in T cell acute lymphoblastic leukemia (T-ALL), pancreatoblastoma (PBL) and neuroblastoma (NBL) using next-generation sequencing and array based technologies. Subsequently, we found novel recurrent SPI1-related fusions in approximately 4% of T-ALL. Importantly, this SPI1 fusions were significantly associated with poor prognosis. In PBL, we found WNT pathway abnormalities in 100% of cases. Uniparental disomy of chromosome 11q was also frequently observed in PBL. In addition, based on the genetic signatures, 6 distinct genetic subgroups were detected in NBL. These subgroups were well correlated with clinical features and outcomes.

② Nephrology group: Our aim is to reveal the

molecular mechanism of pediatric kidney diseases. We revealed novel causative mutations on several proteinuric diseases including idiopathic nephrotic syndrome. We also analyzed pathological changes in glomerulonephritis and found novel mechanism of the phenotypical changes of mesangial cells in glumerulonephritis.

③ Endocrinology and Metabolism group: We analyzed genes and mechanisms involved in endocrinology and bone diseases. We successfully found the responsible gene of a rare congenital disease using next-generation sequencing. We found a novel disease entity caused by LMX1B abnormality. We also determined two novel genetic mechanisms of hereditary rickets.

④ Cardiology group: We performed genome-wide association studies for congenital heart disease and studies to develop a novel treatment for Kawasaki disease using mouse models.

⑤ Neurology Group: The pathogenetic mechanism of acute encephalopathy as well as congenital CNS anomalies such as tuberous sclerosis is investigated. Regarding congenital cytomegalovirus infection, an important and common cause of perinatal brain injury, diagnostic method and treatment are being investigated.

⑥ Neonatology group: Epigenetic changes in cord blood and postnatal peripheral blood of preterm and SGA infants are investigated using epigenome-wide methylation analysis. Neonatal brain function has been investigated using near infra-red spectro-scopy (NIRS) with researchers of Department of Education. A clinical trial of formula supplied with biotin has been conducted with groups of the other Universities. Cytokine profiles have been investigated in order to elucidate pathophysiology of several diseases in perinatal period.

⑦ Immunology group: Research area of interest includes refractory Kawasaki disease and epidemiology of childhood infectious disease.

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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. 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. 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.

The present staff includes one associate professor and chief, one lecturer, and four research associates. 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, and a tumor clinic. Recently, a second-opinion clinic opened to provide careful detailed explanations, and this has received a favorable reception.

Our ward is located on the hospital's second floor, south of the A wing. Other pediatric surgical patients also are admitted to this ward. We have 16 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

A low-invasive operation study group first established under the direction of Professor Iwanaka has been continued since its inception, and has aimed its research at understanding the safety and efficiency of endoscopic surgical techniques in children. This study group also works to develop training tools and instruments for pediatric endoscopic surgery.

In addition, we have initiated joint research efforts to develop anastomotic suture reinforcement and surgical devices, such as clips and staples, by the use of bioabsorbable materials.

The subject of trypsin activation in the intestine of inflammatory bowel disease and the study of cell biological analysis, and a new therapeutic method for lymphangioma, are also being evaluated in ongoing research.

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# Reproductive, Developmental and Aging Sciences

## 3. Aging Sciences

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## Introduction and Organization

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

Since elderly patients tend to have multiple organ disorders, these patients should be taken cared as a whole from multiple points of view. In addition, symptoms, signs and responses to the treatment in the 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.

Specialized services are provided to out-patients on a daily basis in all areas of internal medicine. 352 new and a total of 18,528 patients visited the out-patient clinic in the last fiscal year.

## 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

1. Akiyoshi T, Ota H, Iijima K, Son BK, Kahyo T, Setou M, Ogawa S, Ouchi Y, Akishita M: A novel organ culture model of aorta for vascular calcification. Atherosclerosis 244:51-8, 2016.
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# Surgical Sciences

## 1. Surgery

# Department of Thoracic Surgery

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## History

Study on thoracic surgery has begun since 1916 when symposium on lung surgery was held at annual meeting of Japan Surgical Society. Clinical and basic 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 staffs (Nakajima J, Sato M, Nitadori J, Nagayama K, and Kuwano H), 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 2015, Ministry of Health, Labour and Welfare documented that number of deaths from malignant neoplasms was approximately 370 thousand out of 1.29 million total deaths in Japan. Of them, 74 thousand people were killed by tracheal and 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.

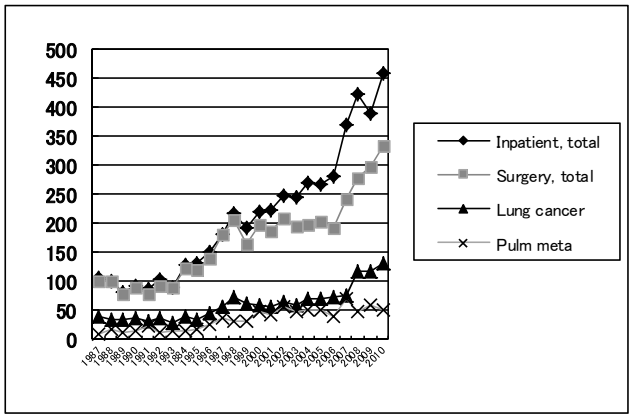
We have performed the modern-style video-assisted thoracoscopy for the diagnosis and treatment of the thoracic disease with less surgical invasiveness since 1992 for safer treatment of older patients with cardiovascular and/or respiratory complications. We currently conduct a standard surgery for clinical stage IA/IB NSCLC, i.e. lobectomy and lymphadenectomy through thoracoscopy: In 2015, more than 90% of patients with NSCLC was the candidate for thoracoscopic surgery in our department. Researches on less-invasiveness, oncological advantage of the thoracoscopic surgery are thus actively done.

We also treat patients with advanced, unresectable NSCLC and those with recurrent NSCLC postoperatively by an immunotherapy. We are now performing a cell-transfer therapy with activated autologous gammadelta T-lymphocytes which has been approved by the Ministry of Health, Labour and Welfare.

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

Thymic epithelial neoplasms, such as thymoma and thymic carcinoma, show broad spectrum in the degree of malignancy. They also associated with para-neoplastic syndromes, such as the myasthenia gravis and the pure red cell aplasia. Although they are relatively rare diseases, we sought to establish the strategies on diagnosis and treatment of these diseases, which are still yet to be determined, from our clinical experiences of more than 200 cases with the diseases in our department. We hosted the annual meeting of Japan Association for Research on Thymus (JART) this year, and we are now actively participating a multiinstitutional study on malignant thymic epithelial neoplasms database led by 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 4 lung transplants to date.




(Figure) Number of inpatient, surgery (total), surgery of lung cancer, and surgery of pulmonary metastasis by year. Pulm meta, pulmonary metastasis

## Academic education

Medical students in the fifth grade have two-weeks' 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. Recently we conducted clinical studies on the immunotherapy with adopted gammadelta- T-cell for the treatment of the patients with unresectable or recurrent NSCLC.

The following are the major themes under research:

(1) Minimally invasive surgeries for thoracic malignant neoplasms.
(2) Identification of small pulmonary lesions through thoracoscopy.
(3) Image analysis of the lung cancer focusing on its degree of malignancy.
(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 and malignant mesothelioma.
(7) Single and multi-institutional studies on thymic epithelial malignant neoplasms.
(8) Single and multi-institutional studies on surgical therapeutics for pulmonary metastasis from colorectal cancer.
(9) Analysis on mechanisms of acute or chronic rejection of the allogeneic lung and trachea after allogeneic transplantation.
(10) Research on donor lung preservation.

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# Department of Cardiac Surgery

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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. Additional clinical team of treatment of advanced heart failure was established to cope with an increasing number of patients who require ventricular assist device treatment. Present staffs are one Chief Professor, one Associate Professor and three Lecturer and eight Associates.

## Clinical Activities

Clinical conference starts at 7:15 am in weekdays. Regular surgery is scheduled on Monday, Wednesday and Friday. Patient round is on Tuesday. Adult patients are hospitalized in the South Wing of 5th floor, and pediatric patients in the South Wing of 2nd floor. Clinics are open Monday through Friday for the follow-up visit as well as for patient referral.

Case volume in recent years has been about 340, which is one of the highest in Japan. We are leading in Japan by showing excellent surgical results. There are eight 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, ventricular assist device implantation, aortic valve sparing root replacement, arch replacement using retrograde cerebral perfusion, 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. Several 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 as advanced medical technology by the Government in 2006. As of March 2017, 80 cases of heart transplantation and more than 250 cases of ventricular assist device implantation were performed in The University Hospital with excellent long-term survival.

## Teaching Activities

We have the chair of systematic review of cardiovascular surgery in the spring term at the 2nd grade of medical course. We also take charge in clinical practice on diagnosis of cardiovascular disease in the autumn term at the 2nd grade. We expose the students to daily clinical works as well as research works during the course of “Free Quarter” and “Research Lab Visit”, which are scheduled in the summer and spring vacations at 1st and 2nd grade. Joint lectures with the Cardiology Department are scheduled 3rd through 4th grades. Each student is assigned one or two cardiovascular surgical cases in the Regular Clinical Clerkship, in which he/she is required to learn preoperative patient evaluation and management, surgical treatment and postoperative care, based on participatory practice. There are also fifteen small key-lectures on cardiovascular surgery. Hands-on practice is provided during the Advanced Clinical Clerkship one-month course in the last months of 3rd grade.

We take charge in core surgical curriculum in the “Super-rotation” postgraduate training. We offer a program in which each resident can learn basic knowledge of cardiovascular disease and surgery, and hemodynamic and respiratory evaluation as well as basic surgical techniques and patient management. Residents who take the course of cardiovascular surgery are required three-year general surgical training for General Surgery Board certification. We have well-developed specialty/ subspecialty training programs to allow the residents to pass Cardiovascular Board Examination by 10-11th 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) mechanism analysis of right heart failure and development of effective pharmacological therapy, 5)

development of versatile suture device, 6) clinical research for new drug for spinal cord ischemia, 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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## 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 the elevation to a department in the graduate school of medicine at our university. Our research activities in both departments have been well organized and ultimately successful by maintaining a close connection.

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 clinical and research activities have for the most part received the cooperation of members in the Department of Metabolic Care and Endocrine Surgery as well as those in other surgical departments at the University of Tokyo.

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.

Junior residents rotate every three months. After completion of their initial training program, they go into a further clinical training program for several consecutive years and become a chief resident. We have also several postgraduate students who are mainly engaged in research work. Their research works are under supervision of the Professor.

## 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, non-transthoracic radical esophagectomy with extended lymphadenectomy (NOVEL) has been applied, which shows less pulmonary complications and good respiratory functions after surgery. New methods of endoscopic full-thickness resection (NEWS) has been developed for some gastric tumor as a collaboration of endoscopy and laparoscopy. The 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 four 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 10-15 patients.

We have our own multidisciplinary disease evaluation systems for inpatients and outpatients, such as endoscopy for upper and lower gastrointestinal tracts, and barium roentgenogram. These multi-disciplinary services provide good opportunities to evaluate the diseases systematically from the surgeon's standpoint.

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. And, 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 more than 150 gastric and 50 esophageal cancer surgeries performed a year, respectively. And, hernia surgery is usually perfomed, also. All residents and medical personnel work many extra hours with high motivation whenever it is necessary 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/transplant/**

## 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 120 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 perform about 170 hepatectomies for HCC and colorectal mets, 80 Whipples, and 20 liver transplantations, mainly from living donors. The overall number of operation is about 510/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 on Hepato-Biliary-Pancreatic Surgery and liver transplantations 50/year. The ongoing topics involve clinical application of ICG fluorescent images, especially for visualization of biliary trees, hepatic tumors, hepatic hemodynamics, 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 pre operative 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. The total number of inpatients was about 1,100 from January 2016 to December 2016. Elective operations are performed on Tuesday,

Wednesday, Thursday and Friday. 1,538 operations were performed in 2016. The numbers of main operations are adrenalectomy 19, nephrectomy 33, partial nephrectomy 38, nephroureterectomy 22, radical cystectomy 28, radical prostatectomy 139, transurethral resection of the bladder tumor (TUR-Bt) 150, transurethral resection of the prostate (TUR-P) 16, laparoscopic surgery 79, and Robot assisted surgery 163 (radical prostatectomy 139, partial nephrectomy 24).

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 22,000 patient-days from January 2016 to December 2016.

## 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, three Lecturers and eleven 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 590 surgically treated inpatients in the year of 2016. On Monday, Wednesday and Friday mornings, pre- and post-surgery conferences are held, and the Professor'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 ulcerative colitis. 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) The mechanism of liver metastasis of colorectal cancer
10) Dendritic cell Immunotherapy for advanced cancer
11) Cancer Immunotherapy targeting to the tumor vessels
12) Role of LPA S1P and productive enzymes in tumor metastasis
13) Lipid metabolism in carcinogenesis and tumor progression
14) Role of peripheral nerve on the growth og gastrointestinal cancer
15) Genetic analysis on sensitivity to chemo-therapeutic agents
16) Hemostasis and fibrinolysis in Oncology
17) Adiponectin and adiponectin receptors in Oncology
18) Intraabdominal chemotherapy for peritoneal metastasis of gastric cancer
19) Pharmacokinetics in intraperitoneal chemotherapy
20) Fibroblast Growth Factor (FGF) in inflammatory bowel disease
21) Genetic analysis of undifferentiated colorectal cancer
22) High Frequency Ultrasonography (HIFU) for solid cancer
23) Quantitative analysis of intraperitoneal cancer cells in peritonitis carcinomatosis
24) Immunomodulation in chemoradiotherapy for locally advanced rectal cancer
25) Autophagy in Oncology
26) Robot assisted laparoscopic colorectal surgery (da Vinci)

27) Postoperative defecation function, urinary function, and sexual function after rectal cancer surgery

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# Department of Vascular Surgery

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## Introduction and Organization

In 1995, a new system for postgraduate education was introduced. The First Department of Surgery was reorganized to form the Department of Vascular Surgery and the Department of Surgical Oncology. The staff of the Department of Vascular Surgery consists of one 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 Department of Vascular Surgery also offers a fellowship in vascular surgery for well-qualified surgeons who have completed their training in general surgery and wish to further specialize in vascular surgery. The Department of Vascular Surgery has a Vascular Surgery Training Program and provides broad reaching experience in technical aspects of vascular surgery, development of surgical judgment, and increasing knowledge about routine and complex

conditions. In addition, the dedicated staff offers multiple opportunities for academic development both along clinical and basic scientific lines.

In the undergraduate education program, the Department of Vascular Surgery plays a role in the systemic and clinical lectures and the bedside learning program for 3rd year medical students, in cooperation with other departments of surgery. In the postgraduate education program, new residents are trained to become qualified surgeons in our department. The Department of Vascular Surgery is involved with the education program of the post-graduate education meeting, which is held monthly. In addition to pre- and post-surgery clinical conferences, the residents are expected to attend research conferences and seminars, which are held periodically.

## Research activities

The Department of Vascular Surgery includes major research laboratories for academic development both along clinical and basic scientific lines. The clinical vascular laboratories are approaching completely non-invasive testing for vascular disorders, analyzing essential physiologic information about the specific problems being addressed. The basic vascular laboratories are actively performing research on endothelial biology, the mechanism of intimal hyperplasia, microcirculation, application of gene therapy to vascular surgery and vascular prosthesis development. Vascular research meeting is held every month on Saturday morning. The following are the major themes under research.

1) Navigation system for less invasive vascular surgery
2) Pathophysiology of the development of the aneurysm
3) Pathophysiology of stent restenosis
4) Analyzing the intercellular transmission of the growth signal in the vascular smooth muscle cells
5) Tissue oxygen dynamics assessed by near infrared spectroscopy
6) Genome wide-association studies for arterio-sclerosis.
7) Pharmacological analysis of microcirculation in in-vivo model
8) Mechanism of arteriogenesis in ischemic limb.
9) Development of a new drug delivery system for therapeutic angiogenesis
10) Hemodynamic analysis after endovascular aneurysm repair
11) Introduction of gene into vascular wall cells by electroporation
12) Application of nano technology for in-vivo gene transfer to vascular wall cells
13) Basic research for arterialization of artificial organ
14) Development of a new method for evaluation of limb ischemia
15) Development of a new machine for auto-evaluation of in-vivo endothelial function
16) Creating strategy for diagnosis of acute aortic syndrome.
17) Analysis of ambulatory system and muscle mechanics in claudicants with peripheral artery disease.
18) Modeling of saccular aneurysm with the computational simulation.

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# Department of Metabolic Care and Endocrine Surgery

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**Homepage**

## Organization

Our section is staffed by one professor, one associate professor, and four assistants. Official activities of our sections are run by same schedule to Department of Gastrointestinal Surgery.

## Clinical Activities

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

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

## Research Acitivities

We investigate wide areas related to breast cancer, thyroid disease, and parathyroid disease. Most of our studies are performed with other good instituteions.

1) Breast cancers originating from the axillary region.

2) Quantification of the hardness of breast cancer using ultrasonography.
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) Cancer epigenesist in thyroid cancer.
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

## Publications


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# Surgical Sciences

## 2. Sensory and Motor System Medicine

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## Introduction and Organization

The Department of dermatology celebrated its 100th anniversary in 1990. Originally it was founded as the Department of Dermatology and Urology, which also encompassed venereology. In 1946, the Department of Dermatology was separated from that of Urology. Regarding venereology, sexually transmitted diseases only related to skin manifestations are now dealt with in our department.

The professor, one associate professors, three lecturers, two hospital lecturer and seven associates take part in inpatient and outpatient cares as well as research and teaching activities. Fifty-two doctors who basically belong to our department are currently out in affiliated hospitals mainly engaged in clinical works there. Additionally, eight staff members are abroad at present, mainly involved in advanced research activities in cell biology and molecular biology.

## Clinical Activities

In the outpatient clinic we see around 200 patients a day. Incisional and excisional biopsies are frequently performed under local anesthesia at the outpatient operation facilities belonging to our department. Clinical and histological discussions by all staff members including Professor and Associate Professors are held regularly, which always gives us invaluable lessons.

Concerning the inpatient clinic, there are about ten staff members under the supervision of the ward-chief. Surgical operations such as removal of malignancies and skin grafting that require general anesthesia are also performed weekly in the central surgical facilities.

## Education

We have twenty dermatologists who are studying in the postgraduate course under the guidance of staff members of our department.

In addition to series of lectures, clinical education is provided for fifth- and sixth- grade medical students, which aims at giving a general introduction for how to make dermatological approaches for diagnosis and treatment, with a stress on learning how to observe and describe a variety of skin eruptions. Actually the students are supposed to see patients in outpatient clinic every day for an entire week, as well as to participate in the inpatient clinic.

## Research

Each specialized outpatient service reflects its own research field in a disease-oriented manner. However, those specialized groups performing their own clinical and research activities are never exclusive, and there are increasing communications with other departments such as internal medicine and blood transfusion service as well as intergroup communications. Recent advanced techniques in cellular, molecular biology and our newly established laboratories, will enable us to organize optimal research conditions.

## Publications


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# 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, 2 lecturer, 1 project lecturer, 6 associates, 4 physicians, and 6 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 trauma, scars and keloids, facial paralysis, hand, replantation, microsurgery, breasts, head and neck reconstruction, cleft lip and palate, craniofacial malformation, congenital anomalies, vascular malformations, lymphedema, and cosmetic surgery including cosmetic dermatology. 1502 New patients visited our department, including 648 patients in emergency. 1426 surgeries were performed. Each week, the professor goes the round of inpatients on Tuesday evening. Preoperative and postoperative conferences and seminar that all members of the department should attend are held on Wednesday evening.

## 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 outpatient clinics, 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. In addition, we accepted 31 observers from foreign countries including China, United Kingdom, United States, Korea, Thailand, Spain, Belgium, Taiwan, Canada, India and Australia.

## Research Activities

Basic and clinical researches are performed in groups. The major research subjects are as follows:

1) Studies on cell isolation from human tissue such as adipose, amnion, and placenta.
2) Studies on mechanism of hypermelanogenesis of the skin.
3) Studies on differentiation induction of human adult stem cells from adipose, amnion, and placenta
4) Characterization of human adult stem cells and dermal papilla cells.
5) Studies on hair regrowth using epidermal stem cells, dermal papilla cells and dermal sheath cells.
6) Clinical studies on fat regeneration using suctioned fat tissue and adipose stromal progenitor cells.
7) Studies on biological function of extracellular matrix taken from human adipose tissue.
8) Studies on angiogenesis using human adult stem cells from adipose.
9) Studies on chondrogenesis and osteogenesis using human fibrin and adipose stromal cells.
10) Studies on molecular mechanisms of vasculogenesis and angiogenesis in the mouse embryo.
11) Studies on molecular pathogenesis of holoprosencephaly using a mouse model.
12) Studies on MMPs and TIMPs expressed in keloid.
13) Studies on the cultured epidermal cells and the cell adhesive function.
14) Studies on clinical application and growth factor extraction of a fluid from continuous suction drainage.
15) Studies on mechanism of biological effects of retinoids on epidermis and dermis.
16) Studies on regeneration of peripheral nerves.
17) Studies on monitoring tissue circulation using flexible optical probe.

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# Department of Oral-Maxillofacial Surgery

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## Introduction and Organization

Department of Oral and Maxillofacial Surgery, commenced by Dr. Hisashi Ishihara in 1900, is one of the oldest departments in Graduate School of Medicine, the University of Tokyo. This department consists of wide variety of specialists, such as oral surgeons, orthodontists and prosthodontists. We handle all diseases in the oral-maxillofacial region, such as congenital anomalies, jaw deformities, benign and malignant tumors, trauma and inflammation. 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: Department 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 chiloplasty and plateplasty 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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## 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, one associate professors, 4 lecturers, 15 associates, 9 medical staff members, 8 senior residents, and 11 part-time teachers.

## 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 13 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 coorporation 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 36,051 patients visited the outpatient clinic in fiscal 2016.

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.

1,339 operations were performed in fiscal 2016. These include 284 spine surgeries, 41 surgeries for rheumatoid arthritis patients, 137 hip surgeries, 267 knee surgeries (including 48 computer-assisted ACL reconstructions, 80 computer-assisted TKA, 42 UKA), 244 hand surgeries, 62 foot and ankle surgeries, 38

pediatric surgeries, 112 surgeries for bone and soft tissue tumor, and 162 trauma surgeries.

The main disorders of cervical spine surgery were myelopathy due to spondylosis or OPLL. We successfully adopted double-door open laminoplasty by splitting the spinal processes for most of these cases. This procedure was invented and developed in our department and is now used nationwide. Difficult operations such as subluxation of the cervical spine due to rheumatoid arthritis, Down's syndrome or cerebral palsy were treated using a navigation system that has been officially approved as a high-level advanced medical treatment.

The spine group is now converting open surgeries to minimum invasive surgeries using endoscopic technique.

The scoliosis group used the navigation system especially for patients with complex deformity. In addition to the conventional correction surgery, growth-assist techniques such as dual growing rods are utilized.

Main operations performed by the rheumatoid arthritis clinic group were total joint arthroplasty. They are using image-free navigation system in total knee arthroplasty operation, which is useful for the accurate placement of the implants.

The hip surgery group treated mainly acetabular dysplasia and osteoarthritis of the hip joint. They performed not only total hip replacements, but also several osteotomies including rotational acetabular osteotomy (RAO). The RAO was originated and established in our department. They conducted a clinical trial for a new artificial hip joint using the MPC polymer in collaboration with the Department of Materials Engineering in Tokyo University.

The knee clinic group developed a new anterior cruciate ligament reconstruction technique using the navigation system based on intraoperative three-dimensional fluoroscopic image to realize ideal graft placement.

The peripheral nerve clinic group has developed "costal nerve transfer to the musculocutaneous nerve" for brachial plexus injury.

The tumor group managed multidisciplinary treatment for musculoskeletal sarcoma including chemotherapy, limb sparing surgery and radiotherapy in coorporation with other departments.

Limb reconstruction operations using external fixators included non-union, leg lengthening and deformity correction. One of the main interests of this group is the development of a system to analyze the mechanical properties of a skeletal system. During this period of analysis, the mechanical properties of the fracture site in vivo are to be evaluated by monitoring the motion of a dynamic pin clamp during simulated walking.

## Research activities

Our research activities cover the full range of the musculoskeletal system medicine, using the in-depth sciences of biology and technology. Especially in the field of molecular biology of bone and cartilage metabolism, we are regarded as being on the leading edge in the world. Basic research is performed under the supervision of the faculty staff members. Five endowment departments take an active role in research activities in close collaboration with our department. Three were established in the 22nd Century Medical Center. They deal with clinical research, which houses the largest clinical database of osteoarthritis patients in the world for the pursue of genomic and etiological research. One department is in the Division of Tissue Engineering, which seeks to develop epochal bone and cartilage regenerative medicine. In the collaboration of the departments, the ROAD (research on osteoarthritis against disability) study has been established as the biggest bone and joint diseases project that covers from basic to clinical researches of the disease. The fourth is founded in the Graduate School of Medicine and the researchers are developing durable artificial joints in cooperation with the Ishihara Laboratory of the Graduate School of Engineering. Furthermore, we collaborate with the Center for Disease Biology and Integrative Medicine (CDBIM), and are developing nonviral gene delivery systems.

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. Recently, we established mouse models for ankle osteoarthritis and intervertebral disc degeneration. We further found novel roles of NF-κB signaling in articular cartilage. We are also engaged in cartilage regenerative research using iPS cells with Dept. of Tissue Engineering.

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 1989. Since then, the department has contributed to Japanese ophthalmology not only by educating a large number of 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 44 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, uveitis and strabismus. Surgeries are performed in the operating theater of the hospital under operating microscopes. Approximately 2100 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 a great potential in training and promoting discussion.

## Teaching activities

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 activities

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 humour 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. Analysis with laser-speckle method of vascular flow in retina and iris
3. Clinical investigation of normal tension glaucoma
4. Drug development in IOP reduction of glaucoma
5. Screening method of glaucoma
6. Tissue engineering of the cornea
7. Molecular analysis of corneal neovascularization
8. Gene therapy for corneal dystrophies
9. Analysis of Meibomian gland with Mibography
10. Analysis of safety of topical eye drops using human corneal epithelial cell sheets
11. Molecular analysis of retinal degenerative diseases
12. Color blindness and visual function
13. Electrophysiological analysis of the effect of drugs on the retina
14. Pathophysiology of age-related macular degeneration
15. Molecular analysis of retinal neovascularization
16. Immuno-hereditary analysis of Harada's disease and Bechet's disease
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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 paresis, vertigo and balance disorders, olfactory disorders and paranasal diseases, voice and speech disorders, taste and swallowing respiratory disorders, aphasia, central auditory disorders and head & neck cancers.

A professor, associate professors, lecturers (assistant professors) and associates participate in surgery, out-patient and in-patient care as well as research and educational activities. Moreover 12 Japanese graduate students and one Chinese foreign graduate student 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, 44 beds are prepared for patients under the supervision of lecturers and senior residents from each subspecialty group including head & neck surgery, middle ear surgery and cochlear implant surgery; voice and broncho-esophagological surgery, and paranasal surgery and other minor surgery. Preoperative and postoperative problems are checked and discussed by each group, the professor's and associate professor's rounds. Approximately 700 operations are performed annually.

Cochlear implant surgery over 400 cases has been actively performed for infants, children and adult patients with profound hearing loss and is very successful to provide new hearing. Head and neck surgery is performed to extirpate malignant tumor with neighboring tissues and reconstruct upper respiratory and swallowing functions at one stage operation cooperating with plastic surgeons. Reconstructive surgery of microtia and atresia to reconstruct external ear is routinely performed with plastic surgeons.

Auditory brainstem response is routinely examined in order to diagnose peripheral and central deafness in neonates, infants and children.

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

## Teaching activities

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

Clinical training is provided for the sixth year class of medical students on a one-to-one basis with staff doctors. They are requested to write reports on a clinical case or a clinical problem. The students participate to see surgery, special clinics and clinical examinations such as otoscope, fiberscope, pure-tone audiometry, auditory brainstem response, and caloric test. Interview with patient is encouraged. They are questioned on many aspects of clinical problems in seminars by professor and associate professor.

## Research activities

Clinical and basic research activities are highly encouraged. Clinical research, which is supervised by senior doctors, is very actively pursued even by young residents. Case reports presentation and writing skills are regarded as important experience in order to develop young doctors' research activity and investigate important findings in patients. The clinical research is related to ear surgery, neurotology, audiology, head and neck surgery, bronchoesophagology and rhinology and is related to case research, clinical statistics and clinical electrophysiology. Basic research is also encouraged to solve essence of clinical problems and to elucidate basic phenomena or anatomical and cellular structures. Our research topics cover:

1) Morphology and neurophysiology of the inner ear focusing on sensory neural deafness: human temporal bone pathology, electron microscopic study in animal models, gene therapy, protein transduction, and nanotechnology
2) Clinical application of otoacoustic emissions and auditory brainstem responses.
3) Histochemistry of olfactory epithelium in development and aging.
4) Clinical neurophysiology of the facial nerves focusing on degeneration and regeneration in patients.
5) Histochemistry of head and neck cancer pathology.
6) The central auditory cortex research using MEG.
7) Auditory brainstem response and speech and hearing after the new born hearing screening.
8) Pathology and electrophysiology of the larynx.
9) Vestibular research on the oculomotor and balance systems in the brain.
10) Vestibular myogenic evoked potentials in cochlear implant and inner ear anomaly.
11) Hair cell physiology in the vestibular end organ.
12) Newborn hearing screening and language development in deaf children.
13) Physiology bone conduction innovation of bone conduction hearing and bilateral hearing.

14) Embryology of middle, inner ear and central auditory system.
15) Therapeutic effects of growth factors on facial nerve regeneration after injury
16) Metabolic conversion of odorant molecules by nasal mucus

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

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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. Sixteen 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 4,000 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 year students from Wednesday to Friday every week. They experience a few patients and learn how to take a patients' history, physical findings, functional evaluation, and how to plan rehabilitation programs. We have introduced a few of elective students for elective clinical clerkship to our collaborating hospitals with specialized rehabilitation ward.

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

## Research activities

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

1) 3D Motion analysis of patients with musculo-skeletal disorders
2) 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

# 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 30 faculty staffs, 12 graduate students and 11 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 12,000. 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 2016 to March 2017, the number of ambulatory patients was about ten thousands; two hundreds and seventy of those were newcomer patients. Currently we have three beds 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 out-patients 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 Emergency and Critical Care 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 2016 fiscal year, we had about 5264 ambulance patients out of total 17936 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

# 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 associate professor, a project researcher, part-time lecturers, a technical specialist, visiting research fellows, 10 doctoral course students, 6 master course students, research associates, 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., work engagement, workaholism, organizational justice, bullying, work-life balance, and the Civility, Respect and Engagement at Work [CREW] program) are also actively investigated. Furthermore, research in the department includes various other topics, such as 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, compared to the situation in the US and European countries, education programs for biostatistics and epidemiological methodology are not sufficient in Japanese universities and graduate schools. Nevertheless the necessity for collaboration between biostatisticians and clinical researchers/ epidemiologists has been to be claimed in recent years. Hence, the central missions of our educational courses are devoted to provide expert knowledge and extensive experience in biostatistics/epidemiology to students 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 and Biostatistics (2 credits) (this class will be separated into “Epidemiology” and “Biostatistics” [2 credits each] in new curriculum from FY2017; the latter is named “Statistics” in medical doctor course)
  2) Applied Mathematics (2 credits)
  3) Statistical Methods and Information Processing Practice (2 credits) (“Biostatistics Practice” in new curriculum, 1 credits)
  4) Design and Analysis of Epidemiological Research, and its Practice (2 and 1 credits) (“Practical Examples in Clinical and Epidemiologic Research” in new curriculum, 1 credits)
  5) Medical Data Analysis, and its Practice (2 credits each)
  6) (New curriculum) Theoretical Epidemiology

- 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 Support 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

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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.

Staff members of the two departments include a professor, two associate professors, an associate, and a technical specialist. All five members, seven undergraduate lecturers and ten graduate lecturers from other organizations, and eight visiting researchers contribute to department teaching and research activities.

We have nine department graduate students. Six

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. Sixteen bachelor theses, twenty-two master theses, and eleven doctoral dissertations were completed between April 2004 and March 2017. Our departments' staff members are also responsible for the following undergraduate and graduate courses.

**Undergraduate Courses**

Required courses

1) Introduction to Biomedical Ethics (Lecture)
2) Health Administration (2 credits, lecture)
3) Biomedical Ethics (2 credits, lecture)
4) Occupational Health and Law (1 credit, lecture)

Elective courses

5) Health & Education (2 credits, lecture)
6) Health Care & Welfare I & II (2 credits, lecture)
7) Field Work for Health Administration (2 credits, practicum)
8) Health Promotion Sciences (1 credit, lecture)
9) Health Policy & Administration (2 credits, lecture)
10) Integrated Lecture of Clinical Medicine, Biomedical ethics (Lecture)

**Graduate Courses**

1) Biomedical Ethics I
2) Biomedical Ethics II
3) Health Promotion Sciences I
4) Health Promotion Sciences II

In addition to these courses, each 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. Graduate courses in Health Promotion Sciences focus on practical study using theories and empirical models for planning, implementation, and evaluation of health promotion programs for the prevention of lifestyle-related disease in the community and workplace.

## Research activities

**Department of Biomedical Ethics**

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

**Department of Health Promotion Sciences**

The main research activity of the Department of Health Promotion Sciences is aimed at health policy proposals concerning health promotion in the community and workplace through experimental and survey research. The main research fields include health behaviors and lifestyle-related disease and QOL. The focus of health behaviors are physical activity, exercise, diet and nutrition, and obesity.

Specific research topics include:

1) Development of effective health promotion programs
2) Assessment of health promotion resources in the community and at the workplace
3) Influence of health behavior change on medical costs
4) Cost-effectiveness analysis for health promotion programs
5) Development of a physical activity questionnaire for the Japanese
6) Studies of the social and physical environments influence on health behaviors
7) Association between family structure and health behaviors in pre-school children
8) Influence of maternal health behavior on children's health behavior
9) Effects of health behavior modification on lifestyle-related disease.
10) Life course epidemiology for women's health
11) Social and physical environmental influences on the health behaviors of people with disease or pain
12) Factors related to health check-ups
13) Characteristics and determinants associated with the uptake of influenza vaccination
14) Influence of employment status on self-rated health

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# Health Sciences and Nursing

## 2. Preventive and Administrative Nursing

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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, Fundamental Nursing III, 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.

**Fundamental Nursing 1 (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.

**Fundamental Nursing 2 (2 credits, lectures)**

This course provides the basics for understanding interpersonal relationships and assessing clients' health. Students will learn the following: 1) theories and practices in communication and 2) physical examination skills essential for health assessments.

**Fundamental Nursing 3**
**(4 credits, lectures, and laboratory practicum)**

This course presents theories and practices in fundamental nursing skills, which are essential for providing nursing care with physiological and psychosocial integrity. Students learn about the nursing process and clients' needs, with case discussions in groups.

**Clinical Practicum in Fundamental Nursing**
**(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. In addition, they will observe nurses working in outpatient clinics and learn the role of nursing in healthcare teams.

**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.

**Nursing Administration Practicum**
**(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 for Nursing Administration and Advance Clinical Nursing.

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

These courses offer a critical analysis of theories in nursing administration related to leadership management, organizational development/career development, quality assurance/improvement, and cost effectiveness/efficient care delivery systems.

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

This course offers an overview of the environment surrounding nursing, political decision-making processes, and public philosophy. Students develop expertise and examine the potentialities of nurses and their legal responsibilities. The political and administrative functional roles of nursing are discussed.

**Seminar (4 credits)**

We have a department seminar every week during which members discuss plans and topics of their own research studies.

## Research Activities

**Environment and Structures to Enable Nurse Administrators to Fulfil their Potential**

We have been examining administrative issues in contemporary nursing. Our main research topic is developing new models for nursing administration/organization development. We inquire to clarify relationships among environmental/structural factors, nurse administrators' competencies/activities, efficacies, and outcome indicators. We have also been examining the methodology for nursing administrators' development.

**Environment and Structures to Enable Nurses to Fulfil their Potentials**

Another main research topic is contributing to the formation of an environment in which nurses/teams mature and succeed. We are studying career development, team/organizational development, team communication, and diversity management.

**Development of Nursing Care Technology**

For more effective nursing care, we have been developing innovative assessment technology using ultrasound and preventive care technology for diabetic foot.

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# Department of Family Nursing

**Professor**

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**Lecturer**

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

**Assistant Professors**

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

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## Introduction and Organization

This department was established in 1992. Four faculty members currently serve the department: a professor, a lecturer, and two assistant professors. Enrolled at present are 9 doctoral students, 6 master's students, 3 research students, 28 visiting researchers, and 3 administrative staff.

## Education

1. Graduate Courses, School of Health Sciences and Nursing (credit hours)
   Advanced Family Nursing I (2)
   Advanced Family Nursing II (2)
   Nursing Consultation (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 Nursing (2)
   Clinical Immunology (1)
3. Undergraduate Courses for Nursing Students in the School of Integrated Health Sciences (credit hours)
   Pediatric and Child Health Nursing (2)
   Clinical Practicum in Pediatric and Child Health Nursing (3)

## Research

In our department, research topics span a variety of topics, focusing on both healthy families and those affected by health problems, and including diverse developmental stages such as perinatal and later-life periods. Our on-going research projects include the following:

1. Mitigation of postpartum depression and prevention of child abuse and neglect;
2. Development of a Pediatric Quality of Life (QOL) Inventory for children with chronic illness and their parents;
3. Support for survivors of childhood cancer including caring of their late effects, special needs education, school reentry and working;
4. Caregiving burden and utilization of respite care services in families of children with medical complexity;
5. Support for dying patients and their families (QOL and family functioning);
6. Livelihood supports for families of elderly people with dementia.
7. Transitional care for children, adolescent and young adult with childhood-onset chronic diseases and their families.

Studies on "Late effects in pediatric cancer survivors" and "Supporting pediatric cancer survivors' reentry to school" 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 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 "transferring into adult health care" and "promoting self-care and autonomy" in patients with child chronic diseases was conducted in 2016. We established a transition outpatient clinic in the University of Tokyo Hospital in June 2016, and provided a transitional care for patients with congenital heart disease, epilepsy, chromosomal abnormality, hematologic disease, and endocrine disease. We also develop 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). Furthermore, we have been developing newly check lists to evaluate long-term follow ups in patients after hematopoietic stem cell transplantation, and supports for school reentry in pediatric cancer survivors. Those studies and activities have been ongoing in interdisciplinary collaboration with health professionals in the University of Tokyo Hospital.

In addition to our research activities, we hold bimonthly Family Care Group Supervisions, whereby deeper understanding of family nursing practices is promoted. In this we aim to enhance the quality of clinical practice and research in family nursing and contribute to the establishment of the science of family nursing.

## Publications


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# Department of Community Health Nursing / Public Health Nursing

**Associate Professor**

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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. At present, there are four faculty members introduced above and 15 graduate course students (9 in master course, 6 in doctoral course) in the department. Also, we accept many visiting researchers from other colleges and institutions.

## Education

1. Undergraduate program, in the School of Integrated Health Sciences

1) Home Health Nursing (2 credits, lectures)
The aim of this class is to have a deep understanding of the social context around the home care patients and the medical, health and welfare system. Students learn the basics of care management, home health care service, and health care system.

2) Community Health Nursing (2 credits, lectures)
In this class, students learn the methodology and basic theory of health promotion, disease prevention and resilience toward society for individuals, families, and groups in community.

3) Home Health Nursing Practice (2 credits, practice)
This program offers opportunities to learn the basis of home nursing and understand the life of home care patients and their family at home-visit nursing station and hospital's department of discharge planning. Basic techniques and the role of nursing through collaboration with other profession are mastered.

2. Graduate program, in the Graduate School of Health Sciences and Nursing (* program for public health nurse curriculum)

1) Advanced Community Health Nursing I
(2 credits, lectures)
This program is to study the health at the community-level and theory and application of the community organization.

2) Advanced Community Health Nursing II
(2 credits, lectures)

This program involves studying issues in home care research and qualitative research methodology for community health nursing.

3) Advanced Community Health Nursing Seminar I, II and Practice I, II (2 credits, practice)
This seminar and practice includes a weekly research meeting and monthly lecture (3rd Friday of each month). At the research meeting, students and faculty members will hold journal readings or research consultation. At the lecture, one or two guest lecturers will introduce their research or clinical topics.
4) Skills for Public Health Nursing I (2 credits, lectures)*
This program aims to provide knowledge and skills that support the techniques required to promote the health of people living in the community. Students will learn basic theory regarding public health nursing.
5) Skills for Public Health Nursing II (2 credits, lectures)*
This program aims to provide knowledge and skills to support the techniques required to promote the health of people living in the community. Students will learn the legal bases and social systems involved in public health nursing.
6) Public Health Nursing I (2 credits, lectures)*
This program involves learning the history, international tendency, and basic theory regarding public health nursing.
7) Public Health Nursing II (2 credits, lectures)*
This program involves learning the ethics and basic theory of public health nursing, and provides an understanding of occupational health nursing.
8) Public Health Nursing III (2 credits, lectures)*
In this program, students will prepare for Public Health Nursing Practice I & II.
9) Public Administration for Nurses (2 credits, lectures)*
This program aims to empower students to discuss health policy from an ethical perspective, development of public health program or policy, and leadership. Students will learn public philosophy, policy-making, and leadership.
10) Public Health Nursing Practice I (1 credit, practice)*
This program intends to generate understanding of the process of public health nurses' continuous care provision or activity, focusing on support for the individual/family and a specific public health issue. In addition, students will visit a clinical setting for school and occupational health nursing practice.
11) Public Health Nursing Practice II (4 credits, practice)*
This program is intended to help further understanding of community assessment and the development of a community program for public health nurses. Students will participate in programs, meetings, and other daily activities held by public health nurses. Throughout their assessment, students are expected to foster their ability to manage and research public health nursing practice.

We hold departmental meetings (journal reading and introduction of research) every Tuesday and monthly research seminars every third Friday to enhance research capacity.

## Research

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, as well as grants from the Ministry of Health, Labour and Welfare, and other foundations.

Ongoing research projects in our department are listed below.

1. 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.

2. 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.

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. Support for families of people with mental illness
Some mental health professionals have recognized that families of people with severe mental illness should be easy to receive support from professionals in the last few years.

5. 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).

6. Support for people with diseases or disabilities
Since the Great East Japan Earthquake on the 11$^{th}$ of March, 2011, we have studied health conditions of affected individuals living in temporary housing in order to improve their QOL in Otsuchi town, Iwate prefecture. We aim to determine the relationship between their health conditions and other related factors.

7. 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 (e.g., use of photo-voice, GIS) and group dynamics.

## Publications


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(14) Masako Kageyama, Sayaka Kobayashi, Keiko Yokoyama, Yukako Nakamura. Partnerships between family caregivers and psychiatric social workers caused by implementation of "Omotenashi-Family Experiences Learning Program" in psychiatric hospitals: Qualitative descriptive analysis of interview data. Japanese journal of psychiatric rehabilitation 20(2), 177-183, 2016

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# Health Sciences and Nursing

## 3. Clinical Nursing

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

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**Assistant Professor (Senior)**

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

**Assistant Professor (Junior)**

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

Naoko Mikoshiba, Ph.D., R.N.

Aki Kawakami, Ph.D., R.N. (June, 2016～)

**Project Assistant Professor**

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Reiko Yamahana, CNS, 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) Developing a clinical education program and educational indicator to improve nurse's clinical judgement competency

Education on clinical judgement is addressed in accordance with the educational guidelines of both basic education and clinical education. However, there are no references to concrete methods on acquiring techniques in the guidelines. For this reason, various teaching methods were looked at, but consistent education for basic education and clinical education could not be found. It can be thought that education at nursing school do not foster the competency of actual practice. In this study, first, the current situation of basic nursing education and clinical education was investigated. An attempt has been made at developing a post-graduate physical assessment training program that aims to strengthen the clinical judgment competency of nurses.

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

## Publications


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# Department of Midwifery and Women's Health

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**Lecturer**

Masayo Matsuzaki, Ph.D., R.N.M., P.H.N.

**Research Associate**

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## Introduction and Organization

The Department of Midwifery and Women's Health was established in 2002.
It has 4 faculty members introduced above, 15 graduate students (6 in master's courses, 9 in doctoral courses), and 2 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 credits, 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) 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) The effect of exercise during pregnancy
This study investigates the effect of exercise on mental and physical health among pregnant women.

3) Lifestyle factors and oxidative stress markers during pregnancy
This study investigates the potential relationships between lifestyle factors and oxidative stress markers during pregnancy to establish optimal oxidative stress markers for predicting a healthy lifestyle for pregnant women.

4) 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.

5) Sleep apnea syndrome during pregnancy
This study investigates the prevalence and risk factors of obstructive sleep apnea (OSA) during pregnancy using a portable device to evaluate sleep and effects of OSA on birth outcomes.

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) Fertility intention among working women
This study investigates the factors related to fertility intention among working women.

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).

## Publications


1. Haruna M, Shiraishi M, Matsuzaki M, Yatsuki Y, Yeo S. Effect of tailored dietary guidance for pregnant women on nutritional status: a double-cohort study. Matern Child Nutr. 2016 Nov 29.
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# Department of Psychiatric Nursing

**Professor**

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**Associate Professor**

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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, 4 doctoral course students, 4 master course students, and research associates.

Our department's mission comprises two elements. One is to provide education and research training in mental health and psychiatric nursing to undergraduate and graduate students in order to prepare students to assume leadership roles in nursing clinical practice, administration, teaching, and research in this field. The other is to conduct clinical research in the fields of psychiatric nursing and advance knowledge and theory through research.

All of the 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; 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


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# Department of Gerontological Nursing / Wound Care Management

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## Introduction and Organization

The Department of Gerontological Nursing was established in June 2003, followed by the establishment of the Department of Wound Care Management in April 2006. These two departments are currently headed by 1 professor and assisted by 1 lecturer, 1 project lecturer, 2 research associates, 1 project research associate, 2 part-time lecturers for undergraduate courses, and 7 part-time lecturers for graduate courses. The student body consists of 6 doctoral course students and 9 master course students. The goal of our department is to achieve "Evidence-based practice and development of gerontological nursing and wound care management".

## Teaching activities

**1. Undergraduate course**

**1) Health Support Practice**

**(W in 2nd yr/ 1 credits)**

Nursing is applied to various social situations, as well as hospital, healthcare center or medical facilities. Nursing is a science of searching the necessary ways for health support and achievement of self-actualization. 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. The program in 2016 included a look into how policies are shaped in order to solve problems confronted in nursing, service for health support, hospital management based on nursing, and the generation of a nursing body of knowledge based on nursing research.

**2) Gerontological Nursing**

**(A2 in 3rd yr/ S1 in 4th yr/ 4 credits)**

The aim of the 3rd year course is for students to understand the physical, psychological, and social characteristics of the elderly population, and to learn fundamental theories of gerontological nursing. The main themes in the 2016 contents were as follows;

a) Practical simulation for gerontological nursing

b) Physical, psychological, and social characteristics of the elderly from a nursing standpoint
c) Gerontological nursing and its theories
d) Geriatric syndrome and nursing (gait disorder, incontinence malnutrition, infection, dementia and pressure ulcer)
e) Future perspectives of gerontological nursing, such as biological nursing, Mimamori engineering, and nursing engineering.
f) Group work

The aim of the 4th year course is to promote an understanding of the ailments and conditions required to provide proper care to the elderly. The main themes in the 2016 contents were as follows;

a) Age-related changes in the physiological system
b) Aging and dementia
c) Aging and osteoporosis
d) Aging and respiratory disorders.
e) Aging and cardiovascular disorders, renal function, hypertension, and stroke
f) Pharmacological management of the elderly
g) Feeding and swallowing difficulty of the elderly
h) Nutritional management of the elderly
i) Relationship and communication skills with the elderly

The above lectures were provided through cooperation from the Department of Geriatric Medicine and other departments at The University of Tokyo Hospital.

**2) Clinical Practice in Gerontological Nursing (S2 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 2016 was supported by the long-term care facility owned by Medical Corporation Tatsuoka.

**2. Graduate course**

**1) Gerontological Nursing I (S1/ 2 credits)**

The main theme of Gerontological Nursing I in 2016 was to understand the latest research related to the care of elderly persons and to discuss future perspectives of 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 for gerontological considerations of the future Japanese community. The main themes in 2016 were as follows:

a) Acute biomedical engineering and rehabilitation for hemiplegia patient
b) Up-to-date information of sarcopenia
c) Care for supporting persons with dementia, and their family
d) The practice of home medical care —interprofessional collaboration in health and social care and the application of information and communications technologies
e) Treatment of pressure ulcers developed in chronic renal disease patients, and nutrition management for patients in perioperative and invasive phases
f) The aim of dysphagia rehabilitation
g) Biological and medical research using the latest technology for micro/nano devices

**3) Wound Care Management I (S2/ 2 credits)**

The main topic of Wound Care Management I in 2016 was learning basic knowledge (basic biology, clinical research, and engineering), which is necessary to understand wound management studies. The topics were as follows:

a) Basic knowledge of wounds and the nursing approach
b) Basics of skin
c) Basics of wounds
d) Basics of molecular and cellular biological research
e) Basics of clinical nursing research
f) Basics of engineering research
g) Molecular and cellular biological approach to nursing

**4) Wound Care Management II (A2/ 2 credits)**

The main theme of Wound Care Management II in 2016 was to obtain deeper insight in our own research knowledge through lectures and discussion by specialists from various basic and advanced research fields. The topics were as follows:

a) Basis and clinical application of ultrasonography in nursing
b) Basics of wound care
c) Basics and application of wound care

d) Pressure redistribution for pressure ulcer prevention
e) Alteration of skin physiology caused by obesity
f) Treatment and care of intractable ulcers

**5) Master's theses**

The following were research themes in 2016:

"Development of a plantar load estimation algorithm for evaluation of forefoot load of diabetic patients during daily walks using a foot motion sensor"

"Development of an automatic puncturing and sampling system for a self-monitoring blood glucose device"

"Development of personalized fitting device with three-dimensional solution for prevention of medical device-related pressure ulcers caused by non-invasive positive pressure ventilation oral-nasal mask"

"Evaluation of comfort associated with the use of a robotic mattress with an interface pressure mapping system and automatic inner air-cell pressure adjustment function"

"Properties of pruritus and related factors among elderly residents of Panti Werdha"

**6) Doctoral theses**

The followings were research themes in 2016:

"Development of a nutritional monitoring method using ultrasonography in the elderly: measuring temporal muscle thickness as an estimate of energy adequacy"

"Development of a pressure ulcer assessment method based on peroxidase and alkaline phosphatase activity detected by wound blotting"

## Research activities

**1. Activity policy**

Our gerontological nursing research focuses on elderly people 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 have been participating with 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 addition, we support the Department of Advanced Nursing Technology which was established in December 2012 as a social cooperation program to promote team nursing intervention and research involving the clinical division, the nursing department, and the nursing departments of 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.

We further promoted a new research framework "Bioengineering Nursing" which consists of nursing biology (which investigates the detailed mechanism of the target phenomenon), nursing engineering (which develops technologies for the clarified target), and nursing translational research (which evaluates the technologies in the clinical filed and further explores new clinical problems). For promoting this research framework to Japanese researchers, we published a book "Bioengineering Nursing" from University of Tokyo Press in 2015. We organized an introductory seminar for bioengineering nursing research involving many nursing researchers and clinical nurses. We furthermore 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.

In December 2016, we organized a seminar for advanced wound care. We shared the latest and advanced knowledge about skincare and wound care with clinical nurses including wound, ostomy and continence nurses, and researchers.

Regarding international activities, our department has been promoting collaborative research with researchers in universities around the world. Our counterparts include: University of California, Los Angeles (CA), Florida University (FL), Curtin University (Australia), and The University of Nottingham (UK). Professor Sanada has been working as Secretary for World Union of Wound Healing Societies and an International Board of Directors for International Lymphoedema Framework.

In February 2017, the Department of Skincare Science, which aims to establish skincare practices to protect vulnerable skin, was established. This department tries to develop new nursing technologies to evaluate and improve the physiological conditions of vulnerable skin due to aging and disease.

**2. Research fields and themes in 2016**

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
- Wound blotting for detecting wound biofilm
- Cutaneous wound healing and diabetes mellitus
- Mechanisms of skin maceration
- Research on scalp care science
- Research on mechanism 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 intravascular catheter by ultrasonography and thermography
- Development of insole-type simultaneous measurement system of plantar pressure and shear force during gait
- Development of fitting device for non-invasive positive pressure ventilation oral-nasal mask using three-dimensional solution

3) Clinical studies
- Novel assessment technologies for pressure ulcers
- Objective evaluation method for wound pain
- Cross-sectional study of diabetic foot (ulcers, callus, fissures, onychomycosis etc.) and its risk factors
- Cross-sectional study of malignant wounds in breast cancer patients and its risk factors
- Survey and international comparison of lymphoedema (collaboration with International Lymphoedema Framework)
- Methods for predicting skin tear development
- Establishment of a novel diagnosis method of latent dysphagia
- Establishment of a novel assessment method of malnutrition using ultrasonography
- Establishment of a novel assessment method of constipation using ultrasonography
- Cross-sectional study of the skin of elderly people in the nursing home
- Cross-sectional study of the skin of obese people

Several awards were given to our research as follows.
- Poster award from 46th Annual Congress of Japanese Society for Wound Healing.

  Takehara K, Minematsu T, Makoto Oe, Noguchi H, Tsunemi Y, Komagata K, Kunie K, Takemura Y, Sanada H. Development of screening tool for tinea pedis by visualization of keratinase for the prevention of diabetic foot ulcers.
- Poster award from 4th Annual Congress of Nursing Science and Engineering.

  Shikama M, Nakagami G, Noguchi H, Mori T, Sanada H. Examination of the position adjustment of non-invasive positive pressure ventilation oral-nasal mask on face using three-dimensional solution for the development of fitting device for prevention of medical device-related pressure ulcers caused by face mask.
- President award from 25th Annual Congress of Japanese Society of Wound, Ostomy, and Continence Management.

  Nozawa K, Tamai N, Amachi H, Kitamura A, Saegusa M, Minematsu T, Sanada H. Relationship between morphological characteristics of pressure ulcer and its occurrence in psychiatric patients.
- President award from 25th Annual Congress of Japanese Society of Wound, Ostomy, and Continence Management.

  Koyano Y, Nakagami G, Tamai N, Tabata K, Sugama J, Sanada H. The dedebridement flowchart estimating the causative external forces of skin tears from its morphology.
- President award from 25th Annual Congress of Japanese Society of Wound, Ostomy, and Continence Management.

  Saegusa M, Nakagami G, Noguchi H, Mori T, Sanada H. Feasibility study of automatic inner air cell pressure adjustment algorithm based on peak interface pressure measured by interface pressure sensor inside the mattress.
- Incentive award from Nursing Science and Engineering 2016.

  Nakagami G, Kubo T, Kawanami H, Iwasaki T, Sanada H. Ceramide delivery to human skin by a ceramide dressing repairs disrupted skin barrier function. Journal of Nursing Science and Engineering. 2015;2(3): 174-9.

・Incentive award from Nursing Science and Engineering 2016.

Oe M, Nagai S, Ikeda M, Oya M, Ohashi Y, Otomo E, Murayama R, Ueki K, Kadowaki T, Komiyama C, Sanada H. Difficulties of the introduction of self-monitoring of blood glucose in elderly diabetic patients. Journal of Nursing Science and Engineering. 2015;2(3): 164-73.

・Article award from Japanese Society of Wound, Ostomy, and Continence Management 2016.

Noguchi H, Oe M, Takehara K, Mori T, Sanada H. Reliability and validity of an on-site measurement and visualization system to measure plantar pressure and shear force in footwear for the education of diabetic patients. J Jpn WOCM. 2015;19(3):327-35.

・Best Teacher's Award from Faculty of Medicine, The University of Tokyo 2016.

Gojiro Nakagami

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3. Mori T, Komichi K, Noguchi H, Umeda-Kameyama Y, Sanada H, Akishita M, Ohe K. Anomaly detection in home monitoring system for the elderly using financial theories. Journal of Nursing Science and Engineering. 2016;3(1):21-30.
4. Tanabe H, Takahashi T, Murayama R, Yabunaka K, Oe M, Matsui Y, Arai UR, Komiyama C, Sanada H. Using ultrasonography for vessel diameter assessment to prevent infiltration. Journal of Infusion Nursing. 2016;39(2):105-11.
5. Dai M, Sato A, Maeba H, Iuchi T, Matsumoto M, Okuwa M, Nakatani T, Sanada H, Sugama J. Dermal structure in lymphedema patients with history of acute dermatolymphangioadenitis evaluated by histogram analysis of ultrasonography findings: a case-control study. Lymphatic Research and Biology. 2016;14(1): 2-7.
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Catheterization among disposable and reusable catheter users. Neurourology and Urodynamics. 2016.
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# International Health

## 1. International Social Medicine

# Department of Global Health Policy

**Professor**

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## Introduction and Organization

Our mission is to improve population health by enhancing accountability and improving the evidence base for global health programs, through the provision of the best possible information and rigorous monitoring and evaluation. The department's members generate knowledge and ideas through their research, strengthen technical and leadership skills through educational programs, and enhance national capacities through collaborative projects, especially in the developing world. As of March 2014 the department, headed by Professor Kenji Shibuya, included the following staff complement: one project professor (Minami Inoue); one associate professor (Stuart Gilmour); two assistant professors (Sarah Abe. Shuhei Nomura; two project assistant professors (Eiko Saito, Md. Mizanur Rahman); two post-doctoral fellows; 12 adjunct lecturers; 12 doctoral students; and nine master's students.

The priority areas of research are:

- 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 G8 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. Furthermore, through the Global Health Entrepreneurship Program (GHE) students are able to develop skills and experience to become future leaders in global health.

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 2014:

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

An evidence-based assessment of the Japanese health system. Ministry of Health, Labour, and Welfare Health and Labour Science Research Grants. PI: Kenji Shibuya

Assessment of Japan's global health policy regarding the 2016 G7 Ise-Shima Summit and its follow-up. Ministry of Health, Labour, and Welfare Health and Labour Science Research Grants. PI: Kenji Shibuya

Global Health Entrepreneurship Program. PI: Kenji Shibuya

AXA Chair on Health and Human Security, AXA Research Fund

Development and evaluation of cancer prevention strategies in Japan. National Cancer Center, National Cancer Center Research and Development Fund. CI: Manami Inoue

Application of recipe-based dietary assessment in Japan. Ministry of Education, Culture, Sports, Science and Technology, Grants-in-Aid for Scientific Research (B). CI: Manami Inoue

Research to establish evidence to benefit health maintenance and improvement including cancer prevention based on multipurpose cohort studies. National Cancer Center Research and Development Fund. CI: Manami Inoue.

Attributable burden of cancer in Japanese: latest estimate and future prediction. Ministry of Education, Culture, Sports, Science and Technology, Grants-in-Aid for Scientific Research (B). PI: Manami Inoue.

A retrospective cohort study to quickly elucidate risk factors and protective factors in middle age dementia patients. Ministry of Education, Culture, Sports, Science and Technology, Grants-in-Aid for Scientific Research (B). CI: Manami Inoue.

Study on establishing appropriate gastric cancer screening provision system based on individual risk. AMED (Project for Whole Implementation to Support and Ensure the Female Life). CI: Manami Inoue.

Analysis of the time-dependent trend of internal exposure examination after Fukushima Nuclear Power Plant accident and factors related to consultation behavior. Program of the network-type Joint Usage/ Research Center for Radiation Disaster Medical Science of Hiroshima University, Nagasaki University, and Fukushima Medical University. PI: Shuhei Nomura

Assessment of the mid- to long-term health effects of Japan's 2011 Fukushima nuclear disaster—toward disaster-resilient health care systems. Toyota Foundation Research Grant Program. PI: Shuhei Nomura.

## Publications


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4. Lin Y, Totsuka Y, Shan B, Wang C, Wei W, Qiao Y, et al. Esophageal cancer in high-risk areas of China: research progress and challenges. *Annals of Epidemiology*. Online first.
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7. GBD 2015 Maternal Mortality Collaborators. Global, regional, and national levels of maternal mortality, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet*. 2016;388(10053): 1775-1812.
8. GBD 2015 Child Mortality Collaborators. Global, regional, national, and selected subnational levels of stillbirths, neonatal, infant, and under-5 mortality, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet*. 2016;388(10053): 1725-1774.
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occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet*. 2016;388(10053):1659-1724.

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13. GBD 2015 SDG Collaborators. Measuring the health-related Sustainable Development Goals in 188 countries: a baseline analysis from the Global Burden of Disease Study 2015. *The Lancet*. 2016; 388(10053): 1813-1850.
14. Chowdhury MRK, Rahman MS, Khan MMH. Levels and determinants of complementary feeding based on meal frequency among children of 6 to 23 months in Bangladesh. *BMC Public Health*. 2016; 16:944.
15. Otsuki S, Nishiura H. Reduced Risk of Importing Ebola Virus Disease because of Travel Restrictions in 2014: A Retrospective Epidemiological Modeling Study. *PLOS ONE*2016;11(9): e0163418.
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25. Japan Global Health Working Group. Protecting human security: proposals for the G7 Ise-Shima Summit in Japan. *The Lancet*. 2016; 387 (10033): 2155-2162.
26. Shin S, Saito E, Inoue M, Sawada N, Ishihara J, Takachi R, et al. Dietary pattern and breast cancer risk in Japanese women: the Japan Public Health Center-based Prospective Study (JPHC Study).

*British Journal of Nutrition*. 2016;115(10):1769-79

27. Saito E, Charvat H, Goto A, Matsuda T, Noda M, Sasazuki S, Inoue M. Burden of cancer associated with type 2 diabetes mellitus in Japan, 2010-2030. *Cancer Science*. 2016;107(4):521-7.
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# Department of Community and Global Health

**Professor, Academic Leader**

Masamine Jimba, MD, PhD, MPH

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Junko Yasuoka, DSc, MPH

Keiko Nanishi, MD, PhD (until July 2016)

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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 inequalities between and within nations on health and development

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 2016, the members of the department include department chair and professor, 3 assistant professors, 4 secretaries, 13 visiting lecturers, 14 doctoral students, 17 master's degree students, 4 research students, and 29 visiting scientists. More than half of the students in this department are international students.

## International Cooperation Activities

As one of our international cooperation activities at the global level, a human security project was conducted in collaboration with the Japan Center for International Exchange (JCIE) and PAHO. The 'health and human security' guideline was published in 2016.

In addition, we contributed to a WHO conference on school health and played a key role to strengthen school health at global level.

Furthermore, we carried out a research project on maternal and child health in Ghana in collaboration with JICA and the Ministry of Health, Ghana. To disseminate the findings of the project, we hosted an international conference in collaboration with JICA. Also, for enhancing human resources, we invited health officers from Ghana, Myanmar, and Nepal to Japan and held workshops on maternal, neonatal and child health.

## Education

The main objectives of our teaching activities are the following two:

1) To train 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 trainings run by JICA and lectures in different 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 is 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 developing countries. We conduct research mainly in developing 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, Bangladesh, Viet Nam, Lao PDR, Cambodia, Indonesia, Ghana, Tanzania, Kenya, Zambia, and Peru.

## Publications

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# International Health

## 2. International Biomedical Sciences

# Department of Human Genetics

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## Introduction and Organization

The Department of Human Genetics was established in 1992. Currently, the department has 1 professor, 1 associate professor, 3 assistant professor, 4 research associates, 7 graduate students, and 6 research assistants/technicians. We also accept a few graduate students from clinical departments 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

The Department of Human Genetics is broadly interested in the human genome diversity, especially in the Asian populations. Specifically, we are using genomic research tools including SNP and micro-satellite analyses, as well as gene expression profiling, to better understand the genetic background of a variety of complex diseases, especially sleep disorders and infectious diseases,

Major research projects:

1) Theoretical and experimental analyses on the genetics of complex diseases, including the development of statistical approaches for susceptibility gene mapping in complex diseases, genomic studies for the understanding of genetic background and pathogenesis of autoimmune diseases, sleep disorders, hypertension, diabetes, as well as for host susceptibility factors to infectious diseases.
2) Development of new methodologies for genome polymorphism and gene expression analyses.
3) Analysis on the genome diversity of Asia-Pacific populations.
4) Analyses on the molecular mechanisms of HLA-associated autoimmune and infectious disorders, by protein functional studies.
5) Genetic analyses combined with epidemiological studies for bone and joint diseases. This study focuses on the elucidation of genetic susceptibility to those, based on four cohorts established in Japan.

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# Department of Developmental Medical Sciences

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## Introduction and Organization

Founded in 1966 as the Department of Maternal and Child Health, our department was the first one established in Japan. With the subsequent expansion of research activities and the foundation of the Graduate School of Medicine, it was renamed in 1998 as the Department of Developmental Medical Sciences. Up to now, it has been engaged in experimental and epidemiologic studies to provide the scientific bases for all the activities to promote the physical and mental health of mothers and children. The experimental studies include those on the nervous and endocrine systems, infection, immunity and metabolism, whereas the epidemiologic studies deal with development, mother-to-child relationship 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 project research associate, one assistant clerk, one technical assistant, fifteen visiting lecturers, eleven visiting researchers, and seven graduate students, including three overseas students.

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, Italy, Greece, China, Taiwan, Korea, Thailand, Viet Nam, Laos, Malaysia, 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 Health Science and Nursing

   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) Seminar in life and environmental sciences
9) Introduction to general health science

2. Graduate course, the Graduate School of Medicine, School of International Health Sciences

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, and acute encephalitis with refractory, repetitive partial seizures.
(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 studies on childhood intractable epilepsy and developmental disorders, such as West syndrome and Rett syndrome, 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) Molecular genetics and biochemistry of inherited metabolic disorders, such as peroxisomal disorders, and of neurodegenerative diseases, such as spinal muscular atrophy.
(7) Studies on the virulence and drug resistance of herpesviruses and poxviruses.
(8) 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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Epidemiology and Infection 2016; 144(2): 346-354.
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# Department of Human Ecology

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## Introduction and Organization

Department of Human Ecology was founded when Kenji Uraguchi was appointed to the professorship of Human Ecology course on April 1, 1965. Following retirement of professor Uraguchi as of March 31, 1966, professor Haruo Katsunuma (appointed also as professor of Public Health Course, School of Medicine) became a joint professor of the Human Ecology Course. Tsuguyoshi Suzuki was appointed as an associate professor and worked in the department until August 31, 1971 when he was transferred to 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 Human Ecology course on April 1, 1972. Professor Koizumi was transferred to Public Health course, School of Medicine on March 31, 1976, and associate professor Shosuke Suzuki served as a department head from April 1 1976 to March 1979.

Tsuguyoshi Suzuki was appointed as a professor of the Human Ecology course as of April 16, 1979. He founded theoretical framework of the current human ecology which is based on studying adaptation mechanisms of humans to environment. After associate professor Shosuke Suzuki was transferred to Faculty of Medicine, Gunma University, as professor on July 31, 1981, Ryutaro Ohtsuka was appointed as an associate professor on September 1. Associate professor Ohtsuka established the methodology of collecting quantitative information on demography, nutrition, and subsistence targeting small-scale populations based on extensive fieldwork, which methodology is still utilized by the 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 in the same year.

Chiho Watanabe was appointed as an associate professor on December 1997. He expanded methodologies that examine relationships between 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 the quantitative research based on fieldwork, he has also been exploring new research topics including

relationship between gut microflora (internal environment) and health. Professor Chiho Watanabe was transferred from the University of Tokyo to the National Institute of Environmental Studies as of April 1, 2017.

We had six research/teaching faculties in FY2016, two of them worked for "UEHAS" program in turn. There are 11 extra-university lecturers delivering lectures in either graduate or undergraduate course. Professor Watanabe holds additional roles in the Integrated Research System for Sustainability Science (IR3S) as well as in the Earth Observation Data Integration & Fusion Research Initiative (EDITORIA).

## Teaching activities

The department is one of the six departments of the School of International Health. Human Ecology Special Lecture I focused on the basic components of Human Ecology such as demography, nutrition, and environment and introducing the notion of human-ecosystem. In "Human Ecology Special Lecture II", emphases were on recent topics and ongoing researches in the field of Human Ecology and related areas. With these classes for the Graduate Students, we tried to describe Human Ecology as a basic component of International Health, and gave examples of the recent issues that have been dealt with and approaches used in this field. The lectures for the Graduate Course were given in English.

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

In addition to these "regular" courses, we have been collaborating with the Graduate School of Engineering of the University of Tokyo in operating the program, "Urban Engineering and Health in Asia (UEHAS)", which been adopted as one of the MEXT-funding "Re-inventing Japan" project (PI= Professor Takizawa, Dept. of Urban Engineering). UEHAS is an educational program at the graduate level entailing credit exchange between the University of Tokyo and six universities in ASEAN countries. Our department has been in charge of coordinating the program from SIH side.

## Research activities

Human ecology is literally the understanding of human population in the context of their respective ecology as well as in the global context. Most of our research tackles the tasks that have been dealt in the field of "Environmental Health" and/or "Population Ecology [of human]", but with more comprehensive and broader context. Therefore, we need to adopt different approaches including fieldwork, experiment, as well as GIS/GPS analyses. Our study fields include Asian-Oceanian (including Japan) rural as well urban communities, focusing on population, nutrition, growth, and environment and sustainability. Experimental studies focusing on the effects of perinatal exposures to heavy metals have been conducted, emphasizing the factors that modify the effects. Almost all the studies require "transdisciplinary" approach, hence, we are collaborating with various domestic and overseas research institutes. What follows is a list of major activities conducted in the past year.

In recent years we also use secondary data for research aiming to elucidate potential effects of environmental exposure (such as air pollution) on health.

1. Environmental contamination by metals and its health impacts in South Asia

   In the As-contaminated area in Myanmar, we recruited pregnant others at clinics and collected biological specimens. We investigated potential effect of arsenic and cadmium exposure on health of mothers and newborns.

2. Adaptation to low-protein diet

Previous studies reported that Papua New Guinea Highlanders show masculine body and do not show clinical symptoms of protein deficiency, although their main diet is sweet potatoes and their protein intake levels is low. To elucidate the biological mechanisms underlying this, we conducted field and experimental studies.

3. Adaptive strategy to aging and depopulation

The population issues (low fertility, aging, population decrease) that Japanese people are now facing are the first problem that humans face at a global scale. Targeting Japanese rural communities, the front-runners of this global issue, we conducted population projection and studies on their food habit, nutritional intake, and subjective perception of health. At the men time, we also conducted a study to categorize original strategies against aging and depopulation that were used in each local community.

4. Double-burden of malnutrition in Indonesia

To elucidate background and mechanisms of the double-burden of malnutrition (coexistence of undernutrition and overweight within the same household), we conducted a survey in a rural and an urban communities in West Java, Indonesia. The prevalence of double-burden households was higher in the urban than in the rural community. It was also suggested that differential nutrient intakes among members of the same household may be one of the factors contributing to double-burden of malnutrition.

5. Study on Fecundity in Japan

Using an internet-based survey we estimated age-pattern of time to pregnancy (duration between discontinuing contraception and conception, used as a measure of fecundity). Additionally, to elucidate which factors can explain the mechanisms of the age pattern of time to pregnancy, we conducted a prospective cohort study targeting pregnancy planners.

6. Health effects of air pollution exposure

Using methodologies of environmental epidemiology, we studied potential effect of air pollution and airborne pollen on health (e.g. mortality, number of clinical visits).

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# Department of Biomedical Chemistry

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## Introduction and Organization

Aim of our department is to contribute to global health and welfare from basic research. Our department, formerly named Biochemistry and Nutrition was renamed on April 1st, 1996 to The Department of Biomedical Chemistry as newly affiliating with Biomedical Science Division of International Health, Graduate School of Medicine, The University of Tokyo. Former Prof. Kiyoshi Kita (Professor Emeritus) has been retired in March 2016, and Dr. Tomoyoshi Nozaki, National Institute of Infectious Diseases, has been assigned as a new professor in October, 2016.

## Teaching activities

Teaching activities in our department cover a broad spectrum of biochemistry-oriented life sciences from premise to frontiers and in either conceptual or experimental point of view

Graduate Course: Biomedical Chemistry I, II

This course is comprised of lectures and seminars to provide basic concepts and newer vistas for understanding biomedical chemistry with special reference to biochemistry and molecular biology. These include the structure and function of biomolecules, metabolism, its regulation, and underlying mechanism at either molecular, cellular and systemic level.

Undergraduate Course: Biochemistry, Molecular Biology, Laboratory Method in Health Science, Basic Life Science, Nutrition, Medical Chemistry, Practice on Medical Chemistry, Parasitology, Life Science and Genome Science I & II, 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

# Department of Social and Preventive Epidemiology

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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

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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 applied course of clinical epidemiology supports the students to build a research hypothesis, design a study, and prepare a study protocol for fund proposal.

The course on health care organization management provides basics of financial accounting, and management frameworks on human resource, strategy, information, and risk, helping the students deepen the knowledge through in-class discussion over real-case scenarios.

The Department accepted 5 master students for the fiscal years of 2016.

## 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

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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 newly developed 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. Patient-provider communication (1): Patient perspective
3. Patient-provider communication (2): Healthcare professional education
4. Communication in group and organization
5. Interpersonal communication skills for behavioral changes
6. Public health communication skills for behavioral changes
7. Evaluation and research in health communication
8. How to write persuasive health materials
9. Media and communication (1): Television
10. Media and communication (2): News paper
11. Media and communication (3): Internet
12. Entertainment education
13. Communicating for policy and advocacy
14. Group discussion

[Health Communication Practice]

1. Coaching
2. Manners in interpersonal relationship
3. MBTI (Myers-Briggs Type Indicator) (1)(2)(3)
4. Mass communication: Media doctor
5. Internet communication (1)(2)

We also provide lectures and practical instruction in medical informatics / economics as part of the PhD program of the Faculty of Medicine. In the undergraduate program, Professor Kiuchi presents a lecture

entitled “Medical Literature Informatics.”

## 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. Based on the analysis of the communication in actual as well as simulated medical encounters, we investigate the relationship of patient and provider characteristics with their communication behaviors, and impacts of the communication on patient outcomes. In addition, we have a seminar to introduce the Roter Interaction Analysis System (RIAS), one of the most widely used tools of the analysis of medical communication,

(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 have developed a measure of health literacy considering the social and cultural context of Japan, and investigated its relationship with patient and provider communication, and patient health behaviors and outcomes.

(4) 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.

(5) 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.

(6) 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

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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 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 the Department of Health and Social Behavior to apply a life-course perspective to a wider range of social conditions and human wellbeing.

The new department intends to further integrate health science (medicine and public health) and social science (economics, sociology, and psychology) to reveal a causal mechanism linking social structure and individual health for realizing health equity as a fundamental goal to human security.

## Teaching activities

The departments offer five courses in the master degree program for public health, and 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 of which 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 ills, and culture and health.
4) Hospital management practicum; using case-method and interactive teaching method, the participant students were provided basic knowledge/skills and real-world decision making training for healthcare organization management in financial accounting, strategic management, and information/risk management.

2. Undergraduate Courses, School of Integrated Health Sciences
   1) Introduction to social survey and practice: The course emphasizes that needs for specific knowledge and subsequent research question define the modes of survey. The course gives the students a virtual situation where a social survey is required to obtain data to support some decision making, e.g. market research situation. The students are asked to define an inquired concept, refine a research question, design the mode of survey, and conduct a small pilot survey within the class. The survey results were reported with some practical implication, and were opened to in-class discussion.
   2) Health sociology:
   3) Health education:
   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) Occupational health management; Lecture series on risk/needs assessment, strategic management of health resource, and health promotion intervention in work place.

FY2016 was the beginning of new curriculum that provides three majors in the School. For Public Health Science track, a new lecture course “integrated lectures of public health science” was offered for the sophomore students expected to join the School. The department was also responsible to offer a new lecture/practicum course on scientific writing, logic, and rhetoric.” As such 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 environ-

ments 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. In 2015-2016, third follow-up for children was conducted to specifically evaluate child’s dietary habit change after a policy intervention in one of participating municipalities, which found a significant improvement in vegetable intake among children in an intervention municipality compared to their counterpart in other cities.

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, with support from AMED and other funding sources. The developed tools are expected to be disseminated and standardized for wider use in municipalities.

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# School of Public Health

## 3. Health Services Sciences

# Department of Clinical Information Engineering

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## Introduction and Organization

Information engineering in Japan places a great deal of weight on computer hardware, software, and data processing. It is a discipline that seeks objective data and emphasizes the conception of new methods of data transfer, storage, processing, and input/output. It also targets research on developing computer devices and systems.

Reviewing the history of the application of computers in medicine, calculating machines for supporting scientists and technologists first appeared in the 1950s. In the 1960s, computers were used for accounting and various statistics. The personal computer appeared in the 1980s and was adopted for personal use in many professions. The systematization of large hospitals, such as university hospitals, pushed ahead rapidly.

In the 1990s, the computer began to be used as a tool to help human thinking, such as in presentations, design, and discovery. When computers became connected to each other through the internet, the distribution of information became very easy and rapid, not only within organizations, but also internationally.

In 2003, a high-quality, "finished" sequence of the human genome was completed. At the dawn of the twenty-first century, bioinformatics appeared as a new discipline, one that uses applied mathematics, informatics, statistics, computer science, and biochemistry to solve biological problems. In medicine, advanced information technologies have been applied to health information infrastructures, electrical clinical guidelines, and knowledge navigation systems.

In response to the needs of the time, the Department of Clinical Information Engineering (CIE) was established at the School of Public Health in April 2007. Its predecessor was the clinical information engineering division of clinical bioinformatics, using Special Coordination Funds for Promoting Science and Technology from 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) Medical Decision-making: We focus on how to improve health outcomes by advancing systematic approaches to clinical decision-making and policy formation in health care using information engineering methodology (IEM), especially electrical clinical guidelines and encoded knowledge.

(2) Data Mining & Knowledge Discovery from Databases: It is necessary to collate heterogeneous information, such as the clinical indications for a drug, drug side effects, pharmacokinetics, metabolic pathways, and drug response genes for single nucleotide polymorphisms (SNPs). These data are distributed and managed in various clinical databases. We are studying ways to integrate distributed biomedical data and knowledge mining with virtualized database technologies, such as auto-indexing and technical term identification algorithms.

(3) 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.

(4) 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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# Endowed Department

# Department of Clinical Epidemiology and Systems

**Associate Professor**

Daisuke Koide, R.Rh., HIM, Ph.D.

**Associate**

Mikio Takanashi, M.D.,Ph.D.

**Researcher**

Yoshiko Mizuno, M.D.,Ph.D.

**Homepage http://cbi.umin.ne.jp/dces/index_e.html**

## Introduction and Organization

The Department of Clinical Epidemiology and Systems was established in 2007, supported by Banyu pharmaceutical company (currently MSD K.K). Our department took over and enhanced the function and infrastructures of the Clinical Epidemiology Division in Clinical Bio-Informatics Research Unit (CBI) which had been led by Professor Ryozo Nagai at the Department of Cardiovascular Medicine (currently President of Jichi Medical University), because the unit had been terminated its five-year program supported by the Japan Science and Technology Agency in 2007 as scheduled. At the time of establishment, the staffs were professor Yamazaki and associate professor Koide.

Our objectives are to develop standards for the transfer of clinical information and improve the quality of clinical epidemiologic researches in the area of life-style related diseases and preventive medicine, because large and longitudinal data are necessary. Through these activities, we evaluate such standards and establish academic foundations of “Clinical Epidemiology and Systems” as well as contribute to professional training in this field which will be more and more required in the future.

In order to facilitate our broad activities, our organization is subordinate to the Department of Cardiovascular Medicine, and works with close collaboration with the staffs in the Center for Epidemiology and Preventive Medicine which was established in 2007 because professor Yamazaki (currently director and professor of clinical research support center) is also the head of the both sections. The staffs of this center overlap with faculty members in the Department of Ubiquitous Preventive Medicine which also took over and enhanced the function and infrastructures of the Genomic Science Division in CBI. Furthermore, these departments work with the Department of Clinical Trial Data Management in the 22nd Century Medical and Research Center, and provide consultation on biostatistics and clinical research. Since Dr. Koide has a background of medical informatics, he develops and systemizes the standards of information in the area of clinical epidemiology in collaboration with the Department of Planning, Information and Management, the University Hospital Medical Information Network (UMIN) Center, the Departments of Epidemiology and Biostatistics, and the Department of Pharmaco-epidemiology.

The first term for five-year passed in March 2012, and the second term has been started since April 2012. When it was renewed, professor Yamazaki moved to the Clinical Research Support Center as director. Also, this department has been supported by the department of Diabetes and Metabolic Medicine (Professor

Takashi Kadowaki) since then. And associate Takanashi and Researcher Yoshiko Mizuno became a member of this department and the Center for Epidemiology and Preventive Medicine. In 2013, the department of Cardiovascular Medicine (Professor Issei Komuro) became the parental department again. In addition to that, the Clinical Research Support Center (Professor Tsutomu Yamazaki) joined as the parental department newly.

Through this cooperation with many departments and centers, we have been conducting education and research. As before, Dr. Koide is an assistant manager of personal information that makes any data of studies regarding human genome or gene anonymous. In the fiscal year of 2016, we received 51 requests and made 3927 samples anonymous.

In addition, our department has been in collaboration with many institutions within and outside the university, since the times of the CBI.

## Teaching activities

On April 13 in 2016, Dr. Koide spoke about “Privacy protection and management in clinical research” at ethical seminar for faculty members and students in the graduate school of medicine, the University of Tokyo. It is mandatory for all researchers in this graduate school to take this seminar once in two years. But foreign researchers who unable understand Japanese well can take alternative e-learning on UMIN. The title of this e-learning is “Principles of Clinical Research and Design” which is provided by MSD K.K. This e-learning is described later.

Also, Dr. Koide lectured to junior students of Integrated Health Sciences, Faculty of Medicine, the University of Tokyo. The title of the lecture was “Drug life-cycle and survey” in the series of "pharmacology and toxicology" on December 20 in 2016. And Dr. Koide gave a lecture which was entitled "Pharmacoepidemiology and Pharmacovigilance by using database" in the series of “Epidemiological study, planning and analysis” for junior students of Integrated Health Sciences, Faculty of Medicine, the University of Tokyo on November 4 in 2016. In addition to that, the same lecture provided by Dr. Koide took place as the series of medical common lectures XXXIII on January 24 in 2017.

Furthermore, Dr. Takanashi has given a lecture on lipid as a part of clinical training for the 5th and 6th grade's students of Medicine, the University of Tokyo since 2013.

And the basic lectures of Medical Writing took place as an intensive course on August 25-26 in 2016, hosted by the non-profit organization of Japan Medical and Scientific Communicators Association, and supported by the three departments of Clinical Epidemiology and Systems, Clinical Trial Data Management, and Ubiquitous Preventive Medicine.

In addition, Dr. Koide gave lectures at the department of Integrated Science and Engineering for Sustainable Society, Faculty of Science and Engineering, Chuo University as “Pharmacovigilance with database” on June 8 and as “Epidemiological research with database” on June 15 in 2016. And Dr. Koide provided a lecture as “-Clinical Pharmacology-, Evaluation of Drug Efficacy and Safety" (3) Pharmacoepidemiology”, which was given to the sixth-grade students at Tokyo University of pharmacy and Sciences on July 7 in 2016. Also, Dr. Koide lectured on “Research Question (RQ) and Pharmacovigilance plan” and “Research Design and Protocol Writing” as Seminars for Regulatory Affairs Professionals at the Pharmaceutical and Medical Device Regulatory Science Society of Japan (PMRJ) which is a non-profit foundation on June 21, 2016. Moreover, Dr. Koide has lectured on ICT literacy as 15 series at faculty of International Liberal Arts, Juntendo University, from October 5 in 2016 to January 25 in 2017.

By the way of public subscription, Dr. Koide has been selected as a research leader of the "collaborative study with universities on development of the e-learning system for clinical research and trial according to the level of skill and profession" for three years since 2012. Although the grant was terminated, this e-learning on UMIN has been continued since 2015. Also, Prof. Matsuyama has obtained the fund by the Agency for Medical Research and Development (AMED), and started to cultivate biostatistician since October 2016. Dr. Koide also participates in this project.

Therefore, we expand our scope of human resource

development for not only clinical epidemiology, but also clinical research and trial.

## Research activities

1) Development of Medical Information Database for Clinical Epidemiology and its validation study

The Ministry of Health, Labor and Welfare and Pharmaceuticals and Medical Devices Agency (PMDA) in Japan started "10 Million patient's medical data project" for improving safety measures, and selected 10 medical institutions including the University of Tokyo. At first, the system development has been launched in the University of Tokyo Hospital. Dr. Koide is in charge of this system development and validation in 2014. In the future, this system infrastructure will be available with other medical institutions for clinical epidemiology.

2) Improving Quality of Health Care

As a member of the quality improvement and assessment committee, clinical pathway committee, and a vice-chair of the committee for quality care at our university hospital, Dr. Koide contributes to assess our quality care and improvement.

3) Standardization of Information in Clinical Epidemiology

As attending Health Level Seven (HL7) and Clinical Data Interchange Standards Consortium (CDISC) which are the international standards development organizations, we study on electronic standards for the transfer pharmaceutical regulatory information, especially focusing on electronic standards for reporting.

4) In Vivo Analysis on Lipid Metabolism

In order to elucidate the pathophysiological role of neutral lipid accumulation in metabolic diseases, we take advantage of mouse models of lipase deficiency and genetic hyperlipidemia, such as hormone-sensitive lipase (Lipe) deficient mice, neutral cholesterol ester hydrolase 1 (Nceh1) deficient mice, Ldlr/Apoe and Apoa5 deficient mice.

Specifically, our recent findings suggest the unprecedented roles of these lipases in diabetic dyslipidemia, non-alcoholic steatohepatitis (NASH) and atherosclerosis. In addition, we recently established an obesity-resistant mutant mouse strain which may lead to the identification of new therapeutic targets to combat obesity-related disorders.

5) Preventive Medicine for Cardiovascular Disease

Cardiovascular disease is one of the main causes of death in Japan and the related medical expenses are bigger than those for cancer. Preventive cardiology, which was initiated by the Japanese medical society in 2000, is now regarded as a key solution to the problem. In light of the need for novel approaches, Dr. Mizuno sought to elucidate mechanisms of atherosclerosis by conducting comprehensive research in healthy subjects. Firstly, we built a database with information from medical check-up, thereafter conducted cross-sectional and prospective studies. One of our recent findings regarding oxidative stress suggests that excessive state of serum iron levels in healthy patients is associated with subclinical atherosclerosis. Dr. Mizuno also elucidated the impact of infection on early atherosclerosis, along with measuring oxidative stress levels in stored blood samples.

6) Serological markers of malignant tumors

Serological markers of malignant tumors such as Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) are known to be associated with metabolic syndrome in several papers. Dr. Mizuno sought to elucidate the relationship between broad range of tumor markers and metabolic syndrome as well as diabetes including impaired glucose tolerance (IGT) by analyzing the data of Japanese who underwent general health screening.

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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.

## 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 (since August 2010, from Shionogi & Co.). 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.

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# Division of Chronic Kidney Disease (CKD) Pathophysiology

**Division Chief (Associate Professor)**

Reiko Inagi, Ph.D.

**Assistant Professor**

Tzu-Ming Jao, Ph.D.

**Postdoctoral fellow**

Kumi Shoji, M.D., Ph.D. (Division of Nephrology and Endocrinology)

Yu Ishimoto, M.D., Ph.D. (Division of Nephrology and Endocrinology)

**PhD Students**

Akira Okada, M.D. (Division of Nephrology and Endocrinology)

Hiroshi Maekawa, M.D. (Division of Nephrology and Endocrinology)

**Visiting Researcher**

Hiroaki Amano, M.D. (Saitama Medical University)

Rikardi Santosa, Msc.

(Faculty of Medicine, Andalas University, Padang, Indonesia)

**Lab Technician**

Ikumi Okuaki, B.S.

Rika Nakamura, Ph.D.

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## Introduction and Organization

In Japan, more than 13 million people suffer from chronic kidney disease (CKD), or roughly one in every eight adults. Why has the number of CKD patients increased so remarkably? One major cause is the sharp increase in the number of people with diabetic nephropathy, which is a complication of diabetes; since 1998, this has been the most important cause among diseases which require incipient dialysis in Japan. Additional causes include the aging of society and other social factors. The kidney is called a silent organ, and CKD progresses without subjective symptoms. It is now evident, however, that asymptomatic CKD which progresses over time carries a number of risks.

One risk is the possible progression of CKD to end-stage renal disease (ESRD), which requires renal replacement therapy. A second risk is the development and progression of lifestyle-related diseases, such as heart attack and arteriosclerosis. The kidneys work closely with the heart and other organs, and a decrease in renal function causes dysfunction of the heart and blood vessels. This adverse impact of the progression of CKD on other organs underlines the importance of the kidneys in maintaining general health. Further,

many researchers have also focused on the vicious spiral of aging and CKD: aging worsens the progression of CKD, while CKD accelerates aging. With our modern lifestyles and the super-aging society, CKD cannot be separated from lifestyle-related diseases, and senility cannot be separated from CKD.

Creating a healthy, long-lived society full of energy and vigor requires that the quality of life (QOL) of the elderly be improved. In turn, total medical expenditures will also be decreased. These are important issues requiring urgent solutions. Against this background, the Division of CKD Pathophysiology was newly established in November 2013 with support from Kyowa Hakko Kirin Co., Ltd. The aim of the Division is to aid and support the CKD control and the creation of a healthy and long-lived society. The Division takes an innovative approach to identifying the pathophysiology of CKD, and works to develop more effective CKD preventive and therapeutic strategies. Through these research activities, our goal is to contribute to the creation of a healthy, long-lived society in which the elderly can live a happy and independent life.

## Major Research Projects

The Division of CKD Pathophysiology works in collaboration with the Division of Nephrology and Endocrinology, a part of The University of Tokyo Graduate School of Medicine (Professor Masaomi Nangaku) to conduct basic and clinical research on CKD pathophysiology, including:

1) Identifying the mechanism of destruction of adaptive signals to various stresses (endoplasmic reticulum stress, ischemia, glycative stress, oxidative stress) in CKD; and using the findings obtained to establish new CKD treatment strategies.
2) Clarifying the mechanism of functional change in renal erythropoietin (EPO)- producing cells, along with the mechanisms of CKD progression and identification of the mechanism of development and progress of renal anemia.
3) Clarifying the impact of kidney aging on CKD progression in super-aging society
4) Identifying factors in the exacerbation of CKD in patients with diabetes, and developing diagnostic and therapeutic drugs targeting such factors.
5) Pathophysiology of uremic toxins on organ crosstalk and impact of uremia management in CKD

## Research Funds (PI)


- Japan Society for the Promotion of Science, Grants-in-Aid for Scientific Research

  **15KT0088** (to **Reiko Inagi**, Analysis of epigenetic regulation of endoplasmic reticulum stress signals on kidney aging),

  **16K15465** (to **Reiko Inagi**, Analysis of pathophysiological significance of D-amino acid in kidney disease)

  **16K09604** (to **Tzu-Ming Jao**, Development of Novel therapeutic approaches targeting ATF-6-mediated metabolic alteration)


## Awards

**Dr. Tzu-Ming Jao** received the Investigators Award of Nagoya Chronic Kidney Disease Frontier.

**Dr. Yu Ishimoto** received the Excellent Award of the 7th molecular Nephrology forum.

**Dr. Yu Ishimoto** received the Young Investigator Award Basic Science (Runner up) in the 15th Asian Pacific Congress of Nephrology (Perth, Australia).

**Dr. Yu Ishimoto** received the Best Abstract Award in the 7th Japanese Society of Pathophysiology in Kidney Disease

**Dr. Akira Okada** received the High Score Abstract Award in Kidney Summit 2016.

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# Department of Molecular Structure and Dynamics

**Project Professor**

Nobutaka Hirokawa, M. D.

**Project Associate**

Tadayuki Ogawa, Ph. 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 Bilogy, Developmental Biology, Histology and Neurocytology.
2) Lecture on Gross Anatomy and Neuroanatomy. to medical students and students of other faculties

II.

1) Laboratory course of Gross Anatomy and Neuroanatomy.
2) Laboratory course of Histology and Histology of the Cenrtral Nervous System.

to medical students and students of other faculties.

In addition we offer a special training course (free quarter) of various kinds of molecular cell biology techniques such as immunocytochemistry, electron microscopy, biochemistry, molecular biology, 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 special and temporal resolution and on these bases try to elucidate functions of molecular motors in vivo combining molecular genetics.

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2. Wang, D., R. Nitta, M. Morikawa, H. Yajima, S. Inoue, H. Shigematsu, M. Kikkawa, and **N. Hirokawa.** Motility and microtubule deploymerization mechanisms of the kinesin-8 motor, KIF19A. ***eLife*** 2016;5:e18101.doi:10.7554/eLife.18101
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# Department of Continence Medicine

**Professor**

Yasuhiko Igawa, M.D.,Ph.D.

**Assistant Professor**

Naoki Aizawa, Ph.D.

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

## 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 path-physiology 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 bed side 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

## Publications


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# Department of Medical Genomics

**Associate Professor**

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## Introduction and Organization

Department of Medical Genomics was established 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 has been run only by the donation from Astellas Pharma Inc. Since April 2013, Department of Cellular Signaling (Professor Hiroyuki Mano) co-supported this Department. Starting from September 2014, Department of Medical Genomics has entered the second 5-year-period by the support from Eisai Co., Ltd. In September 2014, Dr. Yoshihiro Yamashita was promoted to become Associate Professor at Department of Cellular Signaling. In January 2015, Dr. Shinji Kohsaka has jointed Department of Medical Genomics as Assistant Professor.

Department of Medical Genomics enjoys a wide range of research collaboration with many academic institutes within Japan and also from abroad. Especially, this Department is under an intimate collaboration with Department of Cellular Signaling.

## Teaching activities

We jointly take the responsibility for the lectures of Biochemistry as wells as training of Biochemical Experiments for the undergraduate students of the School of Medicine. We also deliver training for graduate students of the Graduate School of Medicine.

## Research activities

Department of Medical Genomics tries to fulfill our goals mainly through two 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* that 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.

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# Department of Life Support Technology (Molten)

**Project Professor**

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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$^{th}$ Oct 2013. Our department played a great important role for management of the meeting as a host.

Current members include a project professor, a project lecturer and a project assistant professor. In addition, an academic support staff is belonging to our department from Global Leadership Initiative for an Age-Friendly Society, Graduate Program in Gerontology.

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.

## 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 Gerontological Nursing for undergraduate course, Taketoshi Mori lectured monitoring system for elderly people. Hiroshi Noguchi also lectured nursing engineering. In addition, Mikako Yoshida supported Gerontological Practical for undergraduate course.
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 Prof. Hiroyasu Iwata, Waseda University and other speakers related to engineering to lecture 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 forth seminar for nursing science and engineering. The staffs in our department had engineering-related lectures and introduction of research using ultrasonography. In addition, our departments hold advanced lecture course about motion sensor.

## 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 attend the Foot Care Outpatient Clinic held by Department of Metabolic Diseases. Mikako Yoshida attended Outpatient Clinic of Urology.

We have been developing a new mattress for pressure ulcer management collaborating with Department of Gerontological Nursing/Wound Care Management. The mattress was called a robotic mattress, and was commercialized from 2016. We developed an automatic inner air-cell adjustment function as a new function of the mattress. The mattress measures body interface pressure continuously using pressure distribution on the mattress and controls amount of inner air-cell pressures. Due to this function, the mattress can control optimal air-cell pressure when maximum interface pressure become lowest. The function realizes automatic adjustment of inner air cell pressure whatever body types and postures people on mattress are. This function leads to appropriate pressure ulcer management. A master course student, who was belonging to Department of Gerontological Nursing/Wound Care Management developed and evaluated this function. In addition, she conducted

case study using the mattress. She wrote master course thesis “Evaluation of comfort associated with the use of a robotic mattress with an interface pressure mapping system and automatic inner air-cell pressure adjustment function” and graduated.

As for the research related to prevention of diabetic foot ulcer, we supported the master course student, who was belonging to Department of Gerontological Nursing/Wound Care Management. She developed a new algorithm. The algorithm estimates perpendicular force on forefoot using only motion sensor data of legs and feet based on body kinematics. She also compared estimated and reference values captured by plantar attached sensor. She also conducted pilot study for two people with diabetes to confirm safety and continuous measurement of the motion sensors.
She wrote master course thesis “Development of a plantar load estimation algorithm for evaluation of forefoot load of diabetic patients during daily walks using a foot motion sensor” and graduated.

In this year, we started a new research theme. It is known that a mask can cause medical device-related pressure ulcer on the nasal bridge under non-invasive positive pressure ventilation therapy. We developed a new device to prevent this pressure ulcer. The 3D shape of face and mask were captured by portable scanner in advance. The gap between the face and mask was calculated. In order to fill this gap, the mold for silicon was designed in 3D CG software, and printed by a 3D printer. Finally, the device made of silicon was created by filling the silicon into the printed mold. We call this device a personalized fitting device. She evaluated the devices with healthy participants. In addition, she conducted a case study for one patient. She wrote the master thesis “Development of personalized fitting device with three-dimensional solution for prevention of medical device-related pressure ulcers caused by non-invasive positive pressure ventilation oral-nasal mask”, and graduated.

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# Department of Youth Mental Health

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## Introduction and Organization

The Department of Youth Mental health was established May 2011. This department is supported by Otsuka Pharmaceutical Co., Ltd. and keeps close relationship with the department of neuropsychiatry.

Youth means the period of time when someone is young, especially the period when someone is a teenager. This period includes the period of puberty and adolescence. This period is unique to human and is very important for developing the ego function. If some critical event happens at this time, the development might be inhibited and this inhibition may cause mental illness. In order to keep this development safely, the close care for teenagers is very useful. Although the importance of mental health of children and adult is emphasized in the history of neuropsychiatry, youth mental health did not attract a lot of attention of psychiatrists and researchers. From the late 20th century, psychiatrists began to notice the importance of youth mental health.

This department has a focus on youth mental health and combines the biological aspect and social aspect of psychiatry. We are trying to create the new concept of the social psychiatry including early intervention and education.

## Clinical activities

We have outpatient clinics especially for the youth. This clinic is a part of neuropsychiatry clinics but treats young people especially suffering from early stage of psychosis. We try to use cognitive and social therapy for those patients and to minimize the use of medication.

Psychiatrists and co medical staffs go to high schools and are engaged in educational activities. School teachers often need some advises about mental health problems happening in schools, we try to assist those teachers as well.

Just after the Great East Japan Earthquake, staffs of the department of neuropsychiatry went to Miyagi prefecture and support the staffs working at Higashimatsushima City. This department also sends staffs and meets the needs of staffs working at Higashimatsushima City.

## Educational activities

Staffs are participating in several kinds of lectures with the staffs of the department of psychiatry. We also manage the mental health research course which is one of the courses of clinical research training program in the University of Tokyo.

## Research activities

Our research field covers Integrative neuroimaging studies for schizophrenia targeting early intervention and prevention (IN-STEP), Tokyo teen cohort study, and the cohort-subsample brain imaging study.

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# Department of Immunotherapy Management

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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, ixelizumb and brodulumab. The Jak kinase inhibitor tofacitinib is only one small molecule. 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 or 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 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 in 2014 at the 22nd Century Medical and Research Centre thanks to donations from Ono Pharmaceutical Co. Ltd., Showa Yakuhin Kako Co., Ltd., and Nippon Zoki Pharmaceutical Co., Ltd. The department is a collaboration among the Department of Orthopaedics, the Department of Rehabilitation Medicine, and the Department of Anaesthesiology and Pain 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.

In April 2014, 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, and Anaesthesiology and Pain Relief Centre (University of Tokyo Hospital). 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

In 2014 the first year after the course's inauguration – we will explore the risk factors that contribute to determining the therapeutic strategy for treating musculoskeletal pain and the prognosis through the following methods:

1) Identify risk factors associated with the onset and exacerbation of musculoskeletal pain through an approach that integrates physical and psychosocial factors as well as biomechanics;

2) Verify the validity of the standard values of screening tools recommended worldwide for their use in Japan; and

3) Evaluate the brain function of people who are on administrative leave due to low back pain, since this phenomenon is a major social problem.

Specifically, we will conduct the following research:

1) Explore the risk factors associated with the onset of low back pain that interferes with work and its conversion to chronicity by using a cohort of about 2,000 persons from four types of occupations (i.e. clerical staff, nurses, sales and marketing associates, and personnel in the transportation industry) and collecting multi-faceted information at baseline;

2) Calculate (on the basis of the prevalence and data from approximately 50,000 people in Japan) the standard values for a screening tool by using a worldwide stratification system that considers psychosocial factors, namely the subgrouping for targeted treatment (STarT) back scoring system, in Japanese subjects. Follow-up surveys at 6 months will be conducted on approximately 2,000 randomly extracted people who have complaints of low back pain, and a weighted psychological validation of the tool will be performed

3) Elucidate the properties of brain functions in patients with LSS compared with a control group composed of healthy subjects. In addition, we will clarify the changes due to interventions by using 18 fluoro-2-deoxyglucose positron emission tomography images of the brain taken before and after therapeutic interventions (e.g. exercise and cognitive behavioural therapy, which are highly recommended worldwide) on approximately 15 cases of refractory low back pain that led to a leave of absence from work.

**Prospects for future research**

We plan to train clinicians with skills in musculoskeletal pain rehabilitation, including specialised exercise therapy and cognitive behavioural therapy for nonspecific low back pain, which is the most frequent type of musculoskeletal pain. By collaborating with the Department of Nursing, we plan to develop simple tools to prevent low back pain, which will be useful in the clinical settings and for industrial hygiene. Moreover, we plan to verify and diagnose the tools' utility and conduct further research on preventive tools and therapeutic programmes.

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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.

## 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 a new transcription factor that controls brown-fat-specific gene program. This factor binds to enhancers near brown-fat-specific genes and facilitates the binding of PPARγ—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 identified another new factor that regulates PPARγ expression through regulation of the cell cycle of adipocytes. Suppression of this factor resulted in inhibition of adipocyte differentiation. Heterozygous knockout mice exhibited smaller adipocytes and were resistant to diet-induced obesity. We expect further investigation on the pathophysiological roles of these factors will provide insights into better understanding of pathophysiology of obesity and development of treatment for obesity.

Impact of inflammatory responses in adipose tissue on obesity-induced insulin resistance

Inflammatory responses in adipose tissue caused by obesity change secretion of adipokines and metabolites, leading to systemic insulin resistance. To clarify the mechanism of these changes, we have extensively investigated expression of genes in human adipose tissues taken from those with a wide range of BMI. We have identified several adipokines, which may initiate the inflammatory responses and subsequent insulin resistance. We are now exploring the role of these adipokines using animal models.

Mechanisms regulating pancreatic β cell function and mass

Progressive decline in pancreatic β cell function and mass has been implicated in the development of type 2 diabetes. We have found that insulin signaling in β cells plays a key role in maintaining β cell mass through insulin receptor (IR)/insulin receptor substrate-2 (IRS-2)/Phosphoinositide-3 kinase (PI3K) by autocrine/paracrine mechanisms using knockout animal models. More recently we have also shown that this pathway contributes to maintaining normal insulin secretion in response to glucose by controlling intra islet communication and exocytotic machinery. Thus, we propose that once insulin secretion is decreased, reduced insulin signaling in b cells causes decreased β cell mass and insulin secretion, leading to decreased β cell mass and subsequent further hypoinsulinemia and hyperglycemia. We seek to identify the strategies for correcting this vicious cycle to cure type 2 diabetes.

Impact of cellular responses in liver to feeding and their disorders on insulin resistance

We have found that feeding transiently promotes endoplasmic reticulum (ER) stress in liver under physiologic condition, and in obesity the ER stress is sustained, leading to inhibition of insulin signaling and insulin resistance. We have also found that insulin signaling suppresses ER stress after feeding and the insulin resistant state decreases insulin signaling and up-regulates ER stress and subsequent further insulin resistance. Recently, we have also shown that IRS-2 is up-regulated in the fasted state to maintain fasting glucose homeostasis and appropriate and prompt metabolic responses to feeding. This is partly regulated by insulin, but we have unraveled that adiponectin contributes to this IRS-2 up-regulation through communicating with adipose tissue-derived substance.

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# Department of Integrated Molecular Sciences on Metabolic Diseases

**Project Associate Professor**

Masato Iwabu, M.D., Ph.D.

**Project Lecturer**

Miki Okada-Iwabu, Ph.D.

## Introduction and Organization

The Department of Integrated Molecular Sciences on Metabolic Diseases (DIMSMD) is devoted to clarifying the mechanisms of onset of lifestyle-related diseases resulting from interactions between genetic and environmental factors in the Japanese population as well as to contributing to the prophylaxis, diagnosis and treatment of these diseases, in response to the drastic increase in the number of diabetic patients which is becoming a major social issue of current interest. In this regard, the DIMSMD strives to establish an accurate method through which to predict risk for the onset of lifestyle-related diseases by tapping into a comprehensive database for genetic and environmental factors for these diseases which is being developed to integrate “Informatics on Genetic Predisposition to Lifestyle-related Diseases” as generated by cutting-edge advances such as single nucleotide polymorphism analyses with “Informatics on Environmental Factors for Lifestyle-related Diseases” that draw on surveys including detailed questionnaires on diet intake. The DIMSMD is therefore expected to make significant scientific and social contributions by providing effective modalities for primary prevention of diabetes, molecular diagnosis of onset of diabetes and its pathology, and optimal treatment of diabetes, and to play a major role in reducing the number of newly onset diabetes as well as in raising the treatment standard for diabetes.

The DIMSMD also aims to develop a system that allows formulas to be developed to predict therapeutic response to drugs as well as their safety to be developed based on information available on environmental and genetic factors including gene expression from patients being treated at University of Tokyo Hospital, and which allows safe and effective use of drugs being developed in patients with lifestyle-related diseases.

The DIMSSMD has set as its final goal the installment of a human metabolic disease tissue bank at University of Tokyo Hospital, which draws on an “integrated database” that offers comprehensive information on gene expression in human hepatic and adipose tissue samples, electronic charts, SNP and lifestyle habits, which will allow validation of molecular targets in actual human diseases, design of a clinical trial system based on SNP and gene expression profiles, development of models for prediction of therapeutic response based on environmental and genetic interactions, identification of molecular targets, discovery of novel therapeutic agents and safe and effective use of drugs thus developed in time.

The DIMSMD is thus engaged in daily research activities and clinical care aimed at contributing to the advancement of health and medical care in the future.

## Research activities

The DIMSMD Research Laboratory aims to elucidate the molecular mechanisms of lifestyle-related diseases

such as the metabolic syndrome, diabetes and cardiovascular disease associated with obesity and to put relevant molecular targets identified in the process to effective use in the treatment of these diseases. Of note, the DIMSMD Research Laboratory has an impressive track record in research in this area, including identification of multiple “key molecules” implicated in lifestyle-related diseases, such as adiponectin receptors, which led to an elucidation of some of the processes through which lifestyle-related diseases develop and progress, based on functional analyses that tap into developmental engineering and RNA engineering. The DIMSMD Research Laboratory has also been credited with discovering that adiponectin is highly active in its high molecular weight form as a ligand to the adiponectin receptors and that its quantitative measurement is useful in the diagnosis of insulin resistance and the metabolic syndrome. Not only that, the DIMSMD Research Laboratory has found that, via the adiponectin receptors, the plant-derived peptide osmotin activates the AMPK pathway which has a critical role in protecting against lifestyle-related diseases. Currently, the DIMSMD Research Laboratory is proactively engaged in the development of definitive treatments for lifestyle-related diseases that draw on ligands specific for the adiponectin receptors.

# Department of Osteoimmunology

**Project Associate Professor**

Kazuo Okamoto, Ph.D.

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Asuka Terashima, Ph.D.

## Introduction and Organization

Bone is a key component of the skeletal-locomotor system and serves as a calcium reservoir regulated by the endocrine system in vertebrates. Bone also acts as the "primary lymphoid organ" that harbors and mobilizes hematopoietic stem cells (HSCs) and immune progenitor cells. Furthermore, the bone and immune systems are closely related through a number of shared regulatory molecules including cytokines, receptors and signaling molecules. Osteo-immunology is an interdisciplinary research field that investigates the shared mechanisms and crosstalks between the bone and the immune systems. Studies on bone destruction associated rheumatoid arthritis (RA) have highlighted regulation of bone by the immune cells and promoted this field. As seen in the clinical benefits of anti-TNF antibody, anti-IL-6 antibody and CTLA4-Ig on inflammation and osteoclast differentiation for the treatment of rheumatoid arthritis, 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 patho-genesis 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 patho-genesis of the diseases, and provide the molecular basis for novel therapeutic strategies. Our achieve-ment would help to improve the welfare and raise the level of medical treatment in the world.

Main research achievements

Immune regulation by osteoblast in the bone marrow

HSCs have the capacity to differentiate into all immune cells, and their activities require extrinsic signals from the microenvironments (niches) in the bone marrow. Various cell types including CXCL12-abundant reticular (CAR) cells, leptin receptor-expressing perivascular stromal cells, $Nestin^{+}$ perivascular cells and neural cells have been shown to be important for HSC maintenance. Although osteo-

blasts 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. These findings suggest that osteoblasts are a potential target of the treatment of systemic inflammatory diseases such as sepsis.

Osteoclast differentiation and RANKL signaling

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 rheumatoid arthritis, 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*. Recently, a fully human anti-RANKL neutralizing antibody has been introduced for the treatment of osteoporosis and skeletal-related events by bone tumors. However, certain reports have suggested that osteoclasts can differentiate independently of RANKL. It has been recently reported that lysyl oxidase (LOX), the collagen cross-linking enzyme, promotes breast cancer bone metastasis by potently inducing osteoclast differentiation in a RANKL-independent manner (Cox et al., *Nature*, 2015). However, it lacks sufficient experimental evidence for the RANKL-independence. By using RANKL-deficient mice, we demonstrated that LOX alone fails to induce osteoclastogenesis, but has the capacity to promote osteoclastogenesis indirectly via induction of endogenous RANKL expression on the mesenchymal cells (Tsukasaki et al., *J Bone Miner Re*s, 2016). These findings not only deepened the understanding of the mechanisms underlying bone metastasis, but also led to the reconsideration of the concept of RANKL-independent osteoclastogenesis.

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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 22nd Century Medical and Research Center in February 2017, which is donated by 10 companies, Development Bank of Japan Inc., Chugai Pharmaceutical Co., Ltd., Baxter Limited, Nihon Medi-Physics Co., Ltd., Medibrain Corporation, Asahi Kasei Medical Co., Ltd., NIPRO Corporation, Toray Medical Co., Ltd., JMS Co., Ltd., and Terumo Corporation, and is cooperating with Department of Cardiac Surgery, Division of Nephrology and Endocrinology, and Department of Clinical Epidemiology & Health Economics as cooperating course.

The social structure has been changing over recent years and it can be assumed that policies related to the medical system and medical industry are at a crossroads in Japan and may undergo dramatic changes in the future. Our department was established to discuss future healthcare systems (medical practices and systems, economy and industry), particularly in terms of theory construction and validation studies pertaining to the "evaluation of the value of the healthcare field" and other topics. Concretely, we promote theoretical and methodological research on health technology assessment, cost effectiveness analysis, and the healthcare industry structure, and aim to evaluate the value of healthcare technologies and healthcare systems. We also promote manpower training programs 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 Biostatistics and Bioinformatics

**Project Professor**

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**Project Assistant Professor**

Sachiko Ono, DDS, MPH.

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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, theJapan funding agency, Agency for Medical Research and Development (AMED), started the Support Program for Biostatiscians from 2016. The aim of this program is as follows (http://www.amed.go.jp/en/program/list/05/01/047.html):

*This program, with the objective of 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.*

*Graduate schools/hospitals develop educational programs that train highly motivated biostatisticians with high expertise and ethics, by enabling the graduate schools / hospitals that properly practice PDCA in the program. In FY2016, 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 Deparment 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 will be established 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 researh, programming, reporting) for conducting clinical research. We will 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 Bio-informatics 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 will issue a certificate along with the Master degree.

**Biostatistics**

statistical inference, categorical data analysis, survival analysis, longitudinal data analysis, Bayesian statistics, multiple comparison prcedure, 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 student receive the OJT at University of Tokyo Hospital and the National Cancer Center. The OJT programs are dveloped 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 a symposiumu for biostatisticians in academia and pharmaceutical companies in order to share and discuss the “state-of-the-arts” of statistical methodolgies. On February 28, 2017, we have implemented the first seminar (Lecturer: Akihiro Hirakawa, Nagoya University and Hajime Uno, Dana-Farber Cancer Institute).

3) Symposium on establishment of Department of Biostatistics and Bioinformatics

Deparment of Biostatistics and Bioinformation was established in the Graduate School of Medicine on March 1, 2017, and the symposiumu was held at the University of Tokyo on February 27, 2017. At the symposium, the AMED support program was introduced and subsequently necessity of nurturing biostatisticians was disucssed as well as the introduction of faculty members . A total of 165 people including students were participated.

## Research activities

The Department of Biostatistics and Bio-informatics consists of one project professor and one project assistant professor. The main reaeach areas are as follows:

1) Statistical methodology and design of clinical trials and epidelimiology

We study on the statistical methodologies and design for streamlining clinical trial and estimating treament 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

Epidemilogy 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 cardio-vascular disorders. Also, several kinds of medical databases are developed rapidely in Japan. It is

important to conduct epidemiological, pharmaco-epidemiological 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 Preventive Medicine for Locomotive Organ Disorders

**Project Professor**

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## Introduction and Organization

The department of department of Preventive Medicine for Locomotive Organ Disorders in 22nd Century Medical and Research Center 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 and in close collaboration with departments of Orthopaedic Surgery and Rehabilitation Medicin. Our department has been established for the epidemiological study to clarify the frequencies and risk factors for locomotive organ disorders including osteoarthritis (OA), osteoporosis (OP) and sarcopenia (SP).

## 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 and 4th follow-ups were performed in 2008-2010, 2012-2013, and 2015-2016, respectively. We will conduct further follow-up surveys.

# Endowed Department

## (22nd Century Medical and Research Center)

# Department of Immunotherapeutics

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## Introduction and Organization

The aim of our Department is to execute basic and clinical research on cancer immunology and immunotherapy and to establish its role in the treatment of cancer. Cancer immunotherapy requires the expansion of functional T cells and/or dendritic cells (DC) that are responsible for the anti-tumor immune response *in vivo*. The GMP-level Cell Processing Center (CPC) was installed in the Department. Peripheral blood mononuclear cells (PBMC) are isolated from the patients and processed in the CPC to ensure that they maintain optimal functionality, or for triggering new functions *in vitro* prior to clinical application. Autologous cells derived from cancer patients are processed for therapeutic use in our CPC in accordance with all current regulations and ethical obligations.

To perform reliable high quality translational research, we designed our Department's facilities literally from the bench to the bedside. The Department consists of three divisions, (1) laboratory for basic and pre-clinical research (2); Cell Processing Center and (3) outpatient clinic. Because these three divisions are situated side-by-side on the same floor, close cooperation between the members of each group can be more easily and better organized. As soon as blood is drawn from the patient at the outpatient clinic, it is directly transferred to the CPC through the pass-box between the two. The cells processed and cultured in the CPC are scrutinized in the laboratory next door to the clinic and CPC regarding their quality and function. Those cultured cells which are approved following this examination are transferred back to the clinic and administered to the patient. The patients are followed-up at regular intervals by the research staff at the laboratory to monitor their immune responses to evaluate the impact of the immunotherapy.

All protocols for cancer immunotherapy performed in our Department are submitted to the institutional review board (IRB). Once approved, the protocols are registered in the UMIN clinical research registration system to provide open access to any interested parties. Because the cells used for treatment are derived from each individual patient; it is difficult to guarantee consistent quality. However, we do everything possible to provide the cultured cells with the best conditions, by means of well-trained specialist staff following standard operating procedures. All these efforts allow us to reliably perform cancer immunotherapy clinical trials in cooperation with many clinical departments of the University of Tokyo Hospital.

Since "The Act on the Safety of Regenerative Medicine" and the "Pharmaceuticals, Medical Devices and Other Therapeutic Products Act" came into effective on November 25, 2014, we registered our cell-processing facility and got approved (DC3140011). All the protocols for cell therapy was also reviewed and approved by institutional committee for the regenerative medicine.

## 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 are underway in our department:

**γδ T cell therapy for advanced cancer**

1. UMIN registration number : UMIN000006128 active, recruiting. Adoptive immunotherapy using zoledronate-expanded autologous γδ T cells for patients with non-small cell lung cancer refractory to standard treatment.
2. UMIN registration number : UMIN000001419 active, recruiting. The efficacy and safety of autologous γδ T cell transfer therapy for esophageal cancer
3. UMIN registration number : UMIN000004130 active, recruiting. Intraperitoneal autologous γδ T cell therapy for refractory gastric cancer with ascites
4. UMIN registration number : UMIN000008097 active, recruiting. Combination of chemotherapy with docetaxel / cisplatin / fluorouracil (DCF) and autologous γδ T cell transfer therapy for esophageal cancer.

**Dendritic cell therapy**

1. UMIN registration number : UMIN000014703 active, recruiting. Safety, efficacy and immunogenicity of concomitant molecular target drug or cytokine therapy and autologous tumor lysate-pulsed dendritic cell therapy in patients with advanced renal cell carcinoma

**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 by means of experiments using animal models and by the immunological monitoring of the patients themselves in clinical research.

## Research activities

All our research activities are directed at understanding the dynamics of the immune response *in vivo* at the molecular, cellular and organismal levels and to develop more effective immunotherapy against cancer. To this end, we perform both clinical immunology in humans and basic preclinical immunology using animal models. We especially focus on the spatiotemporal analysis of anti-tumor immunity in both humans and experimental animals. During the course of each trial, many samples from the clinic are delivered to the research laboratory to monitor immune responses in patients. Tumor-specific immunity is evaluated using standardized immunological assays, such as ELISA, ELISPOT and flow cytometry.

To develop novel immunological interventions, tumor-bearing mice are used to confirm principles believed to be the basis for the new immunotherapy. Using many different TCR-transgenic and human MHC class I-bearing mice we can provide clear answers regarding the antigen-specific immune response. As described above, we pursue a research strategy of going back and forth from the bench to the bedside and from basic to clinical immunology in order to maximize benefit to patients via the rapid application of new knowledge to clinical practice.

## List of Publications

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## Presentation at International conference

1. 2016/4/2, 2nd International Symposium of Lymphedema Surgery and Breast Reconstruction, Tokyo, Japan(Invited), Kazuhiro Kakimi, Cancer Immunity Cycle
2. 2016/10/28, 2016 International Symposiumu for Recent Advances in Cell Therapy and 3rd Annual Meeting of Taiwan Association for Cell Therapy, Taipei, Taiwan(Invited, Symposium), Kazuhiro Kakimi, Personalized Cencer Immunotherapy
3. 2016/12/7, IASLC 17th World Conference on Lung Cancer, Vienna, Austria, WCLC2016 Young Investigators Travel Award 受, Takahiro Karasaki, Kazuhiro Nagayama, Hideki Kuwano, Jun-ichi Nitadori, Masaaki Sato, Masaki Anraku, Akihiro Hosoi, Hirokazu Matsushita, Yasuyuki Morishita, Kosuke Kashiwabara, Masaki Takazawa, Osamu Ohara, Kazuhiro Kakimi, Jun Nakajima, Immunogram for Cancer-Immunity Cycle towards Personalized Immunotherapy of Lung Cancer
4. 2017/2/11, The 32nd Nagoya International Cancer Treatment Symposium, Nagoya, Japan (Invited, Symposium), Kazuhiro Kakimi, An Immunogram for the Cancer Immunotherapy
5. 2017/2/23, ASCO-SITC Clinical Immuno-Oncology Symposium, Orlando, Yasuyoshi Sato, Hirokazu Matsushita, Kazuhiko Mori, Kazuhiro Kakimi and Yasuyuki Seto, Safety, efficacy and immunogenicity of autologous tumor lysate-pulsed dendritic cell vaccination therapy after resection of stage IIA (T2N0, T3N0) esophageal cancer: A phase I trial

# 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. 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.

***Basic Research***

- New strategies to regulate acute rejection and graft arterial diseases in cardiac transplantation.
- New strategies to regulate acute/chronic myocarditis.
- New strategies to regulate acute myocardial infarction and ischemia/reperfusion injury.
- New strategies to regulate restenosis after coronary angioplasty.
- New strategies to regulate atherosclerosis and aneurism.
- New strategies to regulate systolic/diastolic heart failure.
- New strategies to regulate sleep apnea syndrome and circadian rhythm abnormality.
- New strategies to regulate cardio-kidney syndrome.
- New strategies to regulate oral-pathogen induced cardiovascular diseases.
- Development of gene therapies (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.).
- Expanding the use of foods and natural extracts.
- Expanding the application of existing drugs and devices.
- Analysis of angiogenesis using in situ hybridization.

***Clinical Research***

- Gene therapies to prevent restenosis and thrombosis after coronary intervention.
- Pathophysiology of oral disorder and cardiovascular diseases.
- Pathophysiology of sleep apnea syndrome and cardiovascular diseases.
- Pathophysiology of renal dysfunction and cardiovascular diseases.

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**English Review**

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# Department of Joint Disease Research

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## Introduction and Organization

The department of Joint Disease Research was established in 22nd Century Medical and Research Center in 2005, which is an endowment department supported by Chugai Pharmaceutical Co., Ltd. and in close collaboration with departments of Orthopaedic Surgery and Rehabilitation Medicin. Our department has been established for the epidemipological study to clarify the frequencies and risk factors for bone and joint system.

## Research activities

Osteoarthritis (OA) and osteoporosis (OP) are two major public health problems in the elderly that affect activities of daily life (ADL) and quality of life (QOL), leading to increased morbidity and mortality. As the proportion of the aging population is expanding in Japan, there is an urgent need for a comprehensive and evidence-based prevention strategy for musculo-skeletal diseases, including OA and OP. However, few prospective, longitudinal studies have been under-taken, and little information is available regarding the prevalence and incidence of OA and OP as well as pain and disability in the Japanese population. It is difficiult to design rational clinical and public health approaches for the diagnosis, evaluation, and prevention of OA and OP without such epidemiologi-cal data.

We therefore established a large-scale nationwide osteoarthritis/osteoporosis cohort study called ROAD (Research on Osteoarthritis/osteoporosis Against Disability) consisted of total 3,040 participants, of which aims at the elucidation of an environmental and genetic background for bone and joint diseases, represented by OA and OP.

We have completed the baseline study in 2005-2007, then 2nd, 3rd and 4th follow-ups were performed in 2008-2010, 2012-2013, and 2015-2016, respectively.

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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/X-ray computed tomography (PET/CT), 3-tesla magnetic resonance imaging (3T-MRI) system, 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 in order 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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## Introduction and Organization

The Department of Health Care Safety Management was established in December, 2005 within the "22nd Century Medical and Research Center" at the University of Tokyo Hospital based upon contributions by the Tokio Marine & Nichido Fire Insurance Co., Ltd.

Public concern regarding malpractice and the medical related disputes has risen in developed countries accompany several publicized cases such as the public inquiry into children's heart surgery at the Bristol Royal Infirmary and the accidental chemotherapy overdoses occurring at the Dana-Farber Cancer Institute at the end of the 20th century. Reports of the media in our country concerning malpractice and the medical related disputes increased suddenly from 1999. Fears also rose regarding possible criminal prosecutions through the mandatory reporting to the police provided in the Medical Practitioners Law Article 21. Some incidents become targets of investigations although several verdicts resulted in acquittals. Nonetheless, there exist various discussions and some confusion over the intervention of the police authority and criminal procedures into the process of medical treatment.

On another front, in medical related disputes involving civil claims for compensation for damages, many cases have been dealt with and resolved through various measures such as explanation and reconciliation settlement before becoming a lawsuit. In spite of such efforts, the number of civil health care lawsuits has kept increasing from the 1970s (about 100 new

cases received per year) to 2004 (1110 new cases per year), with the pace that has doubled every ten years. Though the number of civil health care lawsuits shows a trend for decrease after 2004, many medical treatment disputes resulted in lawsuits in 2009, with 733 new cases received and 952 cases resolved (preliminary figures).

In our department, while looking straight at the realities of malpractice and the medical related disputes, we aim, from each aspect of the patient, the health care provider, and society, for a healthy rebuilding of the health care system and the recovery of confidence in medical treatment via thinking about the ideal ways to build a better legal system. Together therewith, making the best use of the experience of a state-of-the-art university hospital, we are establishing an approach that promotes mutual understanding by conversations between the patient and the health care provider.

## Research activities

Basic researches concerning both the prevention of malpractice and the honest resolution of medical accidents (including the preventing of disputes and lawsuits) are urgent issues. In addition, we conducted research for the Patient Safety Support Cente as Health & Labour Sciences Research since 2012. In addition, we started “Research on Patient Safety and Physician Sanction Systems in the U.S.” as the joint research under the Pfizer Health Research Foundation. Such research activities are vigorously carried out in our department to return the results widely in society by the development of educational activities.

## Teaching activities

We promote education based on the research results described above for the purpose of training researchers and graduate students in the university.

## Clinical activities

Based on the research results described above, this department supports on-site measures at the place of treatment; and together therewith promote research related to topics transmitted from such sites and education for staff of the site.

*Patient Safety Support Center Comprehensive Support Project

Training and related activities are carried our targeting the personnel of the “Patient Safety Support Centers” established in each prefecture of Japan pursuant to the provisions of the Medical Care Law (a Ministry of Health, Labor and Welfare commissioned project).

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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 approx.imately 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 4,500 hospitals and clinics are participating in NCD with the accumulated data of 6.5 million cases (approximately 1.2 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 Japan SCORE 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, practical analyses, and the development of useful feedback systems. Recently, non-surgical fields such as clinical oncology are also joining NCD and this trend becomes stronger. Our benchmarking projects backed up by NCD's big data will keep driving the quality improvement activities in many healthcare fields.

Increasing numbers of clinical research output has been coming out of the detailed analyses on NCD data in the collaboration of each specialty field. Beside professional societies, pharmaceutical companies as well as medical device firms are now start operating their post-marketing surveillance databases in relation with NCD. Working in between NCD, the firms, PMDA (Pharmaceuticals and Medical Devices Agency), and the related medical societies, HQA helps the project moving forward by giving academic support. Furthermore, HQA has been involved with international research collaboration such as American College of Surgeon's NSQIP and Asian Cardiac Database while contributing to the quality improvement activities in different regions of the world.

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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 carries out educational and research activities on CDM in collaboration with The Department of Biostatistics and The Clinical Research Support Center 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 activate researches on CDM aimed at improving the quality of clinical trials. The other is to produce data managers trained under 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
   - Protocol development
   - Regulatory science
   - Ethics
   - IT
   - 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 stuffs 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 and developing ePRO in collaboration with other universities, pharmaceutical industries, CRO and venders.

We are also supporting several clinical studies which are conducted in the University of Tokyo Hospital. For example, our department functions as a data center for "A clinical study of an oncolytic herpes simplex type 1 (HSV-1) G47delta for patients with castration resistant prostate cancer" which are conducted at Department of Urology in the University of Tokyo Hospital. Moreover, we also have collaborative works outside of University of Tokyo Hospital for several clinical researches. For example, our department support "Exploratory Clinical Trial on Methods and Effects of Tojisha-Kenkyu for Autism Spectrum Disorder" which conducted at Research Center for Advanced Science and Technology, The University of Tokyo and "Psychometric Property of Japanese version of Patient Reported Outcome - Common Terminology Criteria for Adverse Event", "Feasibility study of collecting patient – generated health data using mobile health" which conducted at Department of Pharmacy, Tokyo Medical University Hospital. Finally, as the collaborative department of the Clinical Research Support Center (CresCent), we also involved in their projects as biostatisticians and clinical data mangers.

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# Pharmacology and Pharmacokinetics

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## Introduction and Organization

The research of our laboratory, Pharmacology and Pharmacokinetics, targets quantitative kinetic analysis of efficacy and safety of drugs by applying techniques of modeling and simulation, which have been developed systematically in the field of Pharmacokinetics (PK). It includes some topics in several relating fields such as system pharmacology, quantitative pharmacology, and pharmacometrics. We will survey various issues need to be solved in the current hospital pharmacotherapy and perform various assays of biomarkers and drug concentrations in biological specimens kindly provided from patients. Personalized medicine is one of our important goals to improve current pharmacotherapies by stabilizing efficacy without accompanying unpleasant adverse effects.

The staffs are involved not only in the research and the education in this university, but also in the activity of hospital pharmacy, and are even experienced experts of new drug development in the pharmaceutical industry. Pharmacology and Pharmacokinetics is supported by the Department of Pharmacy in the Tokyo University Hospital. Pharmacology and Pharmacokinetics received kind donations from seven pharmaceutical companies (Takeda Pharma Co Ltd, MSD Co Ltd, Towa Pharmaceutical Co Ltd, Daiichi Sanko Co Ltd, Eisai Co Ltd, Chugai Pharmaceutical Co Ltd, Kyowa Hakko Kirin Co Ltd, Mitsubishi Tanabe Pharma Corporation).

## Education and clinical activities

Although Pharmacology and Pharmacokinetics is not oriented to education and clinical activities in the hospital, the staffs are hospital pharmacists and are involved in the education of graduates and undergraduates in the faculties of medicine and pharmaceutical sciences. Please refer to the annual report of the Department of Pharmacy.

## Research activities

Selected research topics ongoing in Pharmacology and Pharmacokinetics are overviewed in the following.

**Systematic analysis and prediction of drug-drug interaction**

In Japan, more than two thousand drugs are used in pharmacotherapy in hospital. Among them, some combinations would cause unpleasant adverse effects due to pharmacokinetic drug-drug interaction (DDI). We surveyed DDIs caused by inhibition or induction of drug metabolizing enzyme in the literature, and developed a new framework for prediction of various pharmacokinetic DDIs (Hisaka A et al. Pharmacol. Ther., 2010; 125: 230-48. Hisaka A et al. Clin. Pharmacokinet., 2009: 48: 653-66).

By applying this theory, we have been annually making a comprehensive list of drugs which are involved in significant pharmacokinetic DDI in collaboration with the faculty of pharmaceutical sciences. It lists more than 300 drugs which are classified by both clearance pathway and degree of DDI, and is published in a journal which is distributed

to all pharmacies and relating facilities in Japan for free. The list is used for inspection of prescriptions in pharmacies, and in addition, for various purposes in the industry and regulation.

**Establishment of disease progression models using AD as a model disease**

For evaluation of the pathology of Alzheimer's disease (AD), several biomarkers including amyloid-beta peptide (Aβ), tau protein (Tau), and phosphorylated tau protein (pTau) in cerebrospinal fluid, as well as volume of hippocampus, and cerebral FDG-PET have been widely utilized in addition to the score of recognition tests such as ADAS-cog. In ADNI activity, information of these biomarkers was collected extensively to define the progression of AD. However, available information of biomarker is fragmented because of practical restrictions of a period of observation; typically 1~4 years. In contrast, 10~20 years elapse for most patients to be converted from normal to AD. For this reason, relationships among chronological changes of biomarkers and their significance to the disease state have not been fully understood yet. In this study, we applied a new mathematical method, so called SReFT, for estimation of the entire chronological changes of multiple biomarkers from numerous fragmented observations to solve this problem.

**Establishment of the evaluation method for a compound property to induce immune-mediated drug adverse reactions**

Drug adverse reactions are generally classified into two groups. One is an extension of the pharmacological effect, and the other is idiosyncratic drug reaction. The former is dose-dependent and basically predictable based on animal experiments. The latter is not always predictable, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and a drug hypersensitivity. Large part of idiosyncratic drug toxicity is thought to be immune-mediated, and previous reports have indicated the relationships between the development of the idiosyncratic drug adverse reaction and patient human leucocyte antigen (HLA) genotype. In addition, recent reports have revealed that abacavir, which is known to induce severe drug hypersensitivity to patients with HLA-B*57:01 genotype, can bind directly to HLA-B*57:01 protein, leading to the change in peptide repertoire presented by HLA-B*57:01 protein.

The project goal is to establish the method to determine whether a compound interacts with HLA protein and changes presented peptide repertoire or not. To achieve this, construction of HLA protein expression library is necessary. Using the constructed library, differences of peptide repertoire presented by HLA proteins in the presence or absence of a compound can be analyzed. Detection of the difference means that the compound can interact with the HLA protein and possibly induce idiosyncratic adverse reactions.

Activities in our laboratory during two terms (10 years) were finished in fiscal year 2016. Research projects will be continued in Department of Pharmacy.

# Department of Therapeutic Strategy for Heart Failure

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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 thirteen companies.

Recently, right heart failure (RHF) gains recognition as well as left heart failure (LHF). RHF developed after left ventricular assist devise (LVAD) is a critical issue 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 myocardial biopsy once a month in the first year and once a year afterwards. 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 and DuraHeart) or axial VAD (HeartMate II and Jarvik 2000) considering patients' physics and clinical status). We also assisted VAD implantation in affiliate or cooperative hospital in 2012 to establish VAD network in Shinsyu University Hospital, Saku General Hospital, Shinsyu University Hospital, Akita University Hospital,

Gunma Prefectural Cardiovascular Center, and Nagoya Tokusyukai Hospital.

3. Treatment of PH

Although pulmonary arterial hypertension (PAH) was a disease of poor prognosis, the treatment outcome of PAH significantly improved in this decade attributed to a number of newly approved drugs. Now we can use ten agents for PAH including oral, inhaled, subcutaneous and intravenous drugs. Combination therapy of these drugs is increasingly prevalent for the management of PAH. We join the nationwide PH registry to establish optimal treatment strategy for PAH .

## Teaching Activities

We have the chair of systematic review of cardiovascular surgery in the spring term at the 2nd grade of medical course. We also take charge in clinical practice on diagnosis of cardiovascular disease in the autumn term at the 2nd grade. We expose the students to daily clinical works as well as research works during the course of “Free Quarter” and “Research Lab Visit”, which are scheduled in the summer and spring vacations at 1st and 2nd grade. Joint lectures with the Cardiology Department are scheduled 3rd through 4th grades. Each student is assigned one or two cardiovascular surgical cases in the Bed Side Learning, in which he/she is required to learn preoperative patient evaluation and management, surgical treatment and postoperative care, based on participatory practice. There are also twelve small key-lectures on cardiovascular surgery. Hands-on practice is provided during the “Clinical clerkship” one-month course in the last months of 3rd grade.

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

## Research Activities

In order to achieve excellent clinical results and to seek for new possibilities of surgical treatments for heart failure, it is essential for our department of the University to have active research programs in clinical and basic subjects related to assisted circulations and heart transplantation. We created highly active research programs in 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) development of Compact CP external counterpulsation, 3) basic and clinical research on regenerative therapy, 4) establishment of social support system for patients with implantable LVAD. We have organized 4series of clinical trial of implantable rotary blood pump LVAD, EVAHEART, DuraHeart, Jarvik 2000, and HeartMate II since 2007.

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# Social Cooperation Program

# 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. 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.

**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.

**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.

**Methods for clinical samples**

Clinical samples such as blood, urine, feces, and

tissue biopsies vary greatly as compared with controlled animal studies. Furthermore, sampling and storage conditions are not always optimized for lipid analysis. We are developing techniques for handling clinical samples for a practical lipidomics analysis.

**Metabolic flux analysis of lipids**

A simple lipidomics analysis provides large datasets that describe the amount-based profile of lipidome. However, such a 'snapshot' analysis is not sufficient to understand the dynamics of lipid metabolic pathway, because changes in metabolic flux is not always reflected to static amount of metabolites. To overcome this situation, we are developing a flux-oriented lipidomics analysis using stable-isotope tracers.

**Lipid biomarker/lipid mediator discovery using animal models**

Appling the latest lipidomics technologies to the analysis of specimens from the animal models for various diseases including metabolic disease, we are trying to discover novel lipid biomarkers. We also analyze various gene-deficient mice and transgenic mice to seek important lipid markers, lipid mediators, and lipid profiles.

**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.

**Analyses of lipid profile and energy recycling mechanism in *Plasmodium falciparum* (human malaria parasite)**

Human malaria impacts on human health world-wide, resulting in close to430,000 victims each year. However, developments of anti-malarial drug have been hampered by quick emergence of drug resistant parasites. To better understand malaria parasite biology and drug resistance mechanisms, we study molecular pathways of lipid metabolism in parasite and biophysical properties of intracellular membranes that are responsible for malaria protein delivery to the host erythrocyte membrane. Since parasites grow inside human erythrocytes, clean separation of parasites from the host cell and precise biochemical analyses are often difficult tasks. In our laboratory, we combine lipid profiling techniques, a high-resolution fluorescence microscopy, and advanced biophysical analyses to achieve our research objectives.

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# Verbal Analysis of Pathophysiology

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## Introduction and Organization

Department of Verbal 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.

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, Shunji MITSUYOSHI, Ph.D., Project Lecture and three project researchers. Additionally, four guest researchers will attend our department.

## Teaching activities

Shunji MITSUYOSHI, Project Lecturer is 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.

Tokuno Shinichi Project Associate Professor, taking advantage of his expertise, supports the lecture of disaster medicine in emergency medicine.

## 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 pre-stage of society implementation, a prospective study of long-term use by volunteers scheduled to start in 2015 summer.

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

As research for social implementation, we are preparing 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 preparing 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, joint research in the multi-center is planned.

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

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) Cerebral infarction

We are conducting research to capture the change of voice due to cerebral infarction.

3) Others

We are preparing for research for several disease such as mental disorders (PTSD · schizophrenia), neurological disorders (Parkinson's disease), dementia (including; Alzheimer's disease), cardiovascular disease (ischemic heart disease) respiratory disease (COPD · asthma), metabolic diseases (diabetes, gout), for such as otolaryngology disease (tongue adhesion disease, vocal cord polyp), I'm preparing for research.

■ 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.

■ The development of medical devices for voice acquisition and construction of multicenter research infrastructure

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

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# Department of Advanced Nursing Technology

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## Introduction and Organization

The Department of Advanced Nursing Technology was established in December 2012, seeking to develop new academic fields for creating advanced nursing technology based on clinical evidence. Our primary belief is that "Never let patients endure in health care." and we hope that through our activities, we can assist patients to live longer, healthier lives.

Till date, significant difficulties regarding the creation of an advanced nursing technology have created a gap between academic research and clinical needs of the clinical setting. Thus, the strategies of advanced nursing technology could not be applied to hospitals because of their unsuitability to this clinical setting, despite being useful to academic nursing researchers at universities. In contrast, new nursing technologies are often developed because of nurses' experiences in clinical settings with limitations such as the unavailability of scientific processes. Furthermore, systems to promote and support nurses who wish to undertake research in the clinical setting are insufficient.

The Department of Advanced Nursing Technology was established at the University of Tokyo Hospital, supported by Terumo Co., Tokyo, Japan, as a social cooperation program. The United Cooperation Program, established to develop solutions for the abovementioned difficulties and to further the development of nursing technology, comprise the following departments at the University of Tokyo: Department of Gerontological Nursing/Wound Care Management, Department of Nursing, and Department of Diabetes and Metabolic Diseases. We aim to develop a new research model through collaborative research with Tokyo Hospital's Departments of Nursing and Medical examination and School of Health Science at the university. In addition, we aim to disseminate advances in nursing technology based on the needs of clinical practices worldwide. We promote our collaborative research with additional investment from Paramount Bed Corporation since December 2015.

The following are the members from various departments at the University of Tokyo: Ryoko Murayama (Project Associate Professor) and Makoto Oe (Project Lecturer) as well as Hidenori Tanabe (Collaborative Researcher; from Terumo Co.).

## Teaching activities

We advised Master's and PhD course students from the Department of Gerontological Nursing/Wound Care management on matters concerning research planning and practical work. We were involved in providing lectures such as Gerontological Nursing and Gerontological Nursing I, for undergraduates, master course students, or PhD course students with the

Department of Gerontological Nursing/Wound Care management.

The followings were Master's themes in 2016;
"Development of an automatic puncturing and sampling system for a self-monitoring blood glucose device."

## Research activities

**1. Activity policy**

We will develop a new nursing research scheme aimed at identifying clinical needs (i.e., "Never let patients endure in health care."). An interview survey of nurses at the University of Tokyo hospital were therefore conducted to identify clinical needs in the clinical setting. This survey was conducted as a collaborative research with the Department of nursing (University of Tokyo hospital), and is ongoing.

Several research projects are ongoing in our department. These include development of a nursing device for early ambulation and development of a self-monitoring blood glucose device for the elderly. In addition, we are conducting a cross-sectional study of extravasation at our laboratory. These researches are conducted in collaboration with nurses at the University of Tokyo hospital.

We provided nurses with information as the career ladder system in the Department of nursing at the University of Tokyo Hospital. The risk factors for development of diabetic foot disorders and venipuncture are all components of this system.

We offer consultations on research matters and provide guidance on article writing in order to promote nursing research in the clinical setting. A study meeting was planned with the graduate school of the University of Tokyo to educate nurses regarding research. In addition, cross-sectional studies of pelvic floor disorders and diabetic foot were conducted as per the researcher's area of expertise.

**2. Research fields and themes in 2016**

- Investigation of clinical needs in the clinical setting.
- Early ambulation: the management of infusion systems, drains, and catheters for early ambulation and early discharge from the hospital.
- Determining the mechanism of extravasation and development of an indwelling needle for prevention of extravasation.
- Development of a blood glucose self-monitoring device for the elderly.
- Risk assessment for pelvic floor disorders during the postpartum period.
- The diabetic foot and associated risk factors.

Several awards were given to our research as follows.

・Research Award from 4th Conference of Nursing Science and Engineering (Oct.2016)
"Difficulties of the introduction of self-monitoring of blood glucose in elderly diabetic patients."

・Research Award from 25th Conference of Japanese Society of Wound, Ostomy, and Continence Management (Jun.2016)
"Reliability and validity of an on-site measurement and visualization system to measure plantar pressure and shear force in footwear for the education of diabetic patients."

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# Department of Health Services Research

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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 staffs were Taisuke Jo (Project Associate Professor), Nobuaki Michihata (Project Assistant Professor) and Yusuke Sasabuchi (Project Assistant Professor).

## 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 heath 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 2016.

1) Increase in avoidable hospital admissions after the Great East Japan Earthquake.

The Great East Japan Earthquake and subsequent

tsunami and nuclear disaster on 11 March 2011 had a short-term influence on the increase in emergency department visits and hospital admissions due to various diseases. However, it remains unclear whether the earthquake and tsunami disaster affected the long-term health conditions of people in the affected areas.

Therefore, using a national inpatient database in Japan, people's ambulatory care sensitive conditions (ACSCs), which are defined as conditions for which effective management and treatment should prevent admission to a hospital was investigated. We compared the number of admissions for ACSCs before-quake (July 2010 to February 2011) with after-quake (July 2012 to February 2013) periods in the disaster area compared with other areas using a difference-in-differences design. To estimate the impact of the earthquake on admissions for ACSCs, linear regression models with the interaction between periods and areas were used.

No significant difference in difference was seen in preventable ACSCs (where immunization and other interventions can prevent illness) nor chronic ACSCs (where effective care can prevent flare-ups), whereas in acute ACSCs (where early intervention can prevent more serious progression) significant increase was observed (3.3 admissions per 100 000 population; 95% CI 0.4 to 6.3; p=0.028).

Preventable and chronic ACSCs may have increased transiently after the earthquake. However, avoidable admissions due to acute ACSCs were sustained high after the earthquake and tsunami disaster.

2) Association between Dementia and Discharge to Home in Patients Hospitalized for Pneumonia.

Pneumonia is the most common cause of death in dementia, whilst the outcomes of hospitalized pneumonia patients with dementia has been poorly investigated. The objective of this study was to clarify the association of dementia with in-hospital mortality and discharge status in patients hospitalized for pneumonia.

Using the Diagnosis Procedure Combination database, which is a national inpatient database, we retrospectively identified patients who were aged ≥ 60 years and admitted to hospital for pneumonia from May 1 2010 to March 31 2014. We extracted data on sex, age, body mass index, severity of pneumonia, comorbidities including dementia. The outcomes were in-hospital mortality and discharge to home. Cox regression analysis was performed to analyze factors affecting discharge to home.

We identified 397,453 pneumonia patients, including those with dementia (n=38,083) and without dementia (n=359,369). In-hospital mortality was 12.8% and 13.0% in patients with and without dementia, respectively. The proportions of patients discharged to home were 53.6% and 72.2% in patients with and without dementia, respectively. The hazard ratio to return to their home for patients with dementia was 0.69 (95% confidence interval, 0.68-0.70; P<0.001).

In-hospital mortality of pneumonia were identical between patients with and without dementia; however, pneumonia patients with dementia were less likely to return home than those without dementia.

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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# Social Cooperation Program

## (22nd Century Medical and Research Center)

# Department of Ubiquitous Health Informatics

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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.

## 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 un-controlled 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. Thirty-six patients completed the trial and their glycemic control was significantly improved. The effectiveness of this system was also confirmed in Italy. We also devised automatically evaluate system by meal photograph which is healthy food or non-healthy food. It was investigated that healthy food level is able to evaluate with one meal photograph using the system. In addition, we supported the research project of a doctor's degree candidate—"Intention of using an ICT-based self-management tool among patients with diabetes: A cross sectional study"—from the department of Adult Health/Palliative Care Nursing. We plan to conduct a further study to apply the use of the system in clinical environments.

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

We started a clinical study of a smartphone application we call "GlucoNote" for type 2 diabetes and impaired glucose tolerance using ResearchKit by Apple Inc. This application continuously collects data about blood sugar level, blood pressure, weight, active mass and lifestyle including diet, exercise and sleep. This is the first such clinical study in Japan. About 400 patients tried to use GlucoNote during 4-month research. It has potentials for better self-management like decreasing body weight if patients have continued their vital record.

- *HearTily: Self-management and recording application for arrhythmia*

To investigate the association between arrhythmia and lifestyle, we developed the smartphone application "Heartily" for arrhythmic self-management again using Apple's ResearchKit by Apple Inc. About 7,000 participants used Heartily during last one year, a new arrhythmia people were detected in 1.9% of them.

- *Self-management and Recording System for Dialysis (SMART-D)*

The proper intake of water, potassium and phosphorus impacts the survival of dialysis patients, and adherence to fluid-intake restrictions is one of the most difficult aspects of the hemodialysis regimen. So the "Self-management and Recording System for Dialysis" (SMART-D) was developed. It featured the essential indicators for dialysis patients, and its performance was verified. A two-week, non-blinded, non-randomized observational study was conducted. Although there was no change in clinical outcomes after two weeks of using SMART-D, most of the participants reported that using SMART-D helped to improve their lifestyle and self-management. Our study was accepted in this year[2)].

- *Health support study using in Singapore*

For the purpose of preventing development of lifestyle-related diseases in Singapore, a clinical study was performed using a smartphone application to support better self-management of lifestyle. We were brought into this study by NTT Resonant, Inc., which was tasked with it by the Ministry of Internal Affairs and Communications. Our department was asked to supervise the study and analysis the results. We conducted the evaluation of the support application in a clinical trial.

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

Current practice makes it necessary to perform urinalysis with a blood test in order to diagnose the ketoacidosis of diabetes. We plan a clinical study to determine whether clinicians can instead use portable expiration acetone measuring equipment which could measure acetone levels for a diagnosis. The clinical trial was conducted with 120 diabetics, and we investigated the variation of within same participants.

- *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 were confirmed in two participants. It was suggested that atrial fibrillation can be detected by long-term electrocardiogram monitoring.

- *Study of specific health guidance for workers to reduce the risk of diabetes mellitus.*

For the purpose of reducing the risk of diseases mellitus, a clinical study was performed using ICT system (smile data vision) to support better self-management of lifestyle. We were brought into this study by Meiji Yasuda Life Health Insurance Association. Our department was asked to supervise the study and analysis the results. Currently, the participants are measuring their blood glucose level, blood pressure, body weight and dietary intakes at home and will continue to analyze at the University of

Tokyo to promote the improvement of the subject's lifestyle habits.

- *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 management of PHR. We surveyed 5,000 people and got responses from about 2,500 people, and analyzing the result.

***Future directions***

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

## Publications in English

(Original article)


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# University Hospital

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## Introduction and Organization

Clinical Laboratory Center consists of 12 doctors, a chief technologist, and 80 technicians, and is divided into the following sections. The second - 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 and blood and urine sampling. In 2016, 232,532 outpatient blood sampling were performed in this section.

The 2nd Section

This section deals with clinical biochemistry and immuno-serology tests. In 2016, over 5,335,679 serum enzyme tests (such as AST and ALT), and 594,535 immunological tests were performed.

The 3rd Section

This section deals with laboratory hematology and DM-related tests, gene analysis tests and urinalysis. In 2016, 1,259,635 samples were examined for complete blood cell counts, cell surface marker analysis, prothrombin time, fibrinogen, glucose, and HbA1C tests, and 247,789 urine samples were examined.

The 4th Section

This section deals with physiological tests, including circulatory, pulmonary, and neuromuscular function ones. In 2016, 47,399 ECG, 25,490 pulmonary function tests, 11,384 echocardiography tests, 17,544 abdominal echography tests, and 10,258 EEG were performed.

The Hospital Ward Section

This section has been recently founded and is in charge of laboratory tests, mainly ECG, for seriously-ill, hospitalized patients. In the future, this section is going to be further expanded since there is so much

demand from clinical doctors.

## Teaching activities

Lectures are given to the fourth, fifth 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. Laboratory practice teaching 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. 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) platelet biology, iii) the clinical significance of reticulated platelets and immature platelet fraction, iv) novel biomarker in liver diseases, v) genetic testing, vi) bioactive peptides, especially adrenomedullin, vii) oxidative stress and organ injury, viii) analysis of cardiac functions using ultrasound, ix) elucidation of abnormality in epigenetics in cancer and its clinical application, and x) 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 in the Old Central Building till December 1987. The center moved to the new Central Clinical Service Building 1 on January 1988, when the surgical center had 14 ORs including one bio-clean room. The administrative staff included 4 doctors, 75 nurses, 6 technical officials, 5 part-time employees. 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 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 B Building in October 2001. After the merger, the number of elective operations markedly increased and became over 7,300. The 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 orthopedic outpatients was diverted for the general OR, which was used for the short-stay and day surgery. In April 2014, we renovated an OR into a hybrid OR that is equipped with advanced interventional imaging system for the patients undergoing interventional surgical treatment.

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 the year 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.

A total of 8,485, 9,550, 9921, 9,944, 10,394, 10,170, 10,752, 11,235, 11,150, 10,960 and 11,161 operations were performed in 2006, 2007, 2008, 2009 2010, 2011, 2012, 2013, 2014, 2015 and 2016 fiscal year, respectively. The number of operations in 2016 fiscal year counts for approximately 1.8 times comparing to that in 2001.

These days more and more patients undergo the operation, using endoscopic technique, 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 with positive test for the particular types of pathogenic bacteria, such as tuberculosis, MRSA, pseudomonas aeruginosa, HBV, HCV and HIV.

## Scope of Activities of Surgical Center

The surgical center covers broad area of clinical activities ranging from the operation schedule to the education of the medical students and healthcare workers, and research on healthcare practices.

## Operation Schedule

All operations of in-patients are performed in 23 ORs at the surgical center. Computer system has been utilized in order 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 in 2000.

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

The SPD system and the progressive patient care system started in the Ward A Building and Central Clinical Service Building 2 in order to improve the workflow of hospital in October 2001. 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 MIDCAB operations for CABG and endovascular treatment for heart anomalies such as ASD and VSD. More recently, the robotic surgery has started at the surgical center.

Healthcare-Associated infections (HAI) are critical issues in the surgical center. It is mandatory to educate how to prevent HAI and occupational infections. As the number of operation of the patients with emergence and re-emergence infectious diseases such as HIV and tuberculosis has increased, all health care staff in the surgical center are required to adhere to the principles of standard precautions and transmission-based precautions.

## Teaching Activities

The following lectures or seminar are given to the undergraduates and postgraduates 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 recently 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 a scrub nurse or a circulating nurse. 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 wall 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 transplantation surgery, open-heart surgery, neurosurgery and robotic surgery.

There is also a training course to clinical 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-job training are given to the non-nursing staff including technical officials and temporary employees and performed when they start their careers in 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 summarized and stated in the manual. Lectures are also given to the senior technical officers and temporary 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 robot-assisted operation
5) Efficient use of human resources
6) Introduction of advanced operation assisted by the microscopy and/or laparoscopy
7) Proper management of equipment of endoscopy-assisted surgery
8) Centralization of the live video images of the surgical field
9) Management of surgical devices using UID
10) Perioperative infection control and prevention related to the sterilization
11) Maintenance of the surgical environment in the OR
12) Maintenance and management of the surgical equipment
13) Perioperative nutritional management of the surgical patients
14) Others

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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, 73 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 2002. 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, 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 and vascular interventional procedures except for cardiac and peripheral arterial studies. All of these examinations are performed under the requests of clinicians. Over one hundred and fifty 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 four of 3-Tesla scanners every day. Diagnostic and interventional procedures are performed using six angiographic units.

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, C-11, N-13 and O-15. 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 multileaf 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 enabled 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.

# Department of Pharmacy

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**Lecturer**

Tappei Takada, Ph.D.

**Research Associate**

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## Introduction and Organization

We have 9 faculty members, 72 pharmacy staffs, and 10 graduate students and 2 undergraduate students from the faculty of pharmaceutical sciences (as of January 1st, 2017). In addition, project associate professor (Masashi Honma, Ph.D.) is involved in our work.

## 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 (2,461 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 a member of ICT.

Statistical Data (fiscal year 2016)
Number of items on in-hospital formulary: 2,461
Number of prescriptions (ps.) filled or preparation (pp.) (annual)

| | | |
|---|---|---|
| out-patients | : | 416,282 ps. |
| (outside | : | 347,579 ps.) |
| (inside | : | 68,703 ps.) |
| out-patient chemotherapy | : | 12,478 ps. |
| in-patients | : | 238,190 ps. |
| injection drugs | : | 209,470 ps. |
| IVH | : | 3,948 ps. |
| chemotherapy | : | 10,208 pp. |
| TDM consultations (annual) | : | 16,128 pp. |

Numbers of hospital pharmaceutical cares (annual): 18,186 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 2016, 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 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 continued by shortening the period to half a year. In 2016, 11 pharmacists finished this course.

In addition, we are promoting life-long education of pharmacists in the local area by holding regular technical workshops and seminars.

## Research

It is evident that the molecular function of particular element cannot always be assigned to only one function at whole body level, because one to one simple correspondence is not common in our body. It is also true that the understanding of the relationship between drug and its ultimate target is not sufficient to predict the pharmacological/toxicological effects. We need to understand not only the detailed molecular machinery of drug target, but also its environment surrounding the target (ex. other associated proteins, signaling molecules, etc.), where and when it works, and finally how it behaves as functional unit in our body. This is a basic idea trying to understand "living body" as "system". By further promoting this idea to "system pharmacology", we will be able to identify a molecular target which is related to the pharmacological/toxicological output in clinical situation or even at early drug development stage. Based on such concept, following projects are now ongoing:

1. Elucidation of the molecular mechanism which controls *in vivo* disposition of lipids / bile acids / uric acid, and establishment of new therapy for life-style related diseases based on those integrated understanding.
2. Elucidation of the dynamic regulatory mechanism of bone resorption / bone formation, and establishment of new therapy for bone metabolic disease based on those integrated understanding.
3. Establishment of the way to quantitative understanding and prediction of pharmacological-effect and adverse-effect of drugs directed against particular molecular target. Finally, these outputs would be feedbacked to early drug development stages.
4. Elucidation of the molecular mechanism related to the adverse effect of drugs using large-scale "-omics" analysis. Finally, the quantitative information would be applied to develop strategies to prevent / treat the adverse effect.
5. Absolute quantification of factors determining the pharmacokinetic profiles of drugs and its application to clinical pharmacokinetics and pharmacology field.

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# Delivery Unit

**Professor**

Tomoyuki Fujii

**Associate Professor**

Takeshi Nagamatsu

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## Organization

The Delivery Unit of the University of Tokyo Hospital is organized by one professor, one associate professor and about 10 fellows. All the staff members are taking part in research activities of reproductive endocrinology, gynecologic oncology, or perinatal medicine, as well as being engaged with in-patient and out-patient care for pregnant women including the activities in the delivery units.

## Activities

Total number of delivery cases was 1065 (22 weeks later) in 2016.

Recently, cases of obstetrical emergencies like abruptio placentae, eclampsia and uterine ruptures transported from neighboring hospitals have been increasing. Three doctors and three midwives are on duty every night. Our service is an important part of Tokyo Metropolitan Service System for Maternal Welfare and Perinatal Medicine.

## References

[See Department of Perinatal Medicine.]

# Rehabilitation Center

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## Introduction and Organization

The physical therapy service started in 1963 at the University of Tokyo Hospital, and then expanded to include occupational therapy and social work section. In 1966 this service was converted to the central rehabilitation service department as a part of the Central Diagnostic and Therapeutic Service Department. The Central Rehabilitation Service became an independent unit in 1970. After the reorganization of the University of Tokyo Hospital according to major organic classification in 1998, outpatient clinic as rehabilitation medicine was installed. The formal title of our unit was changed from the Physical Therapy Department to the Rehabilitation Department by the budget measures in the fiscal year 2001, and we integrated the related personnel categories, which belonged to the orthopedic surgery department and the physical medicine department.

At the present time 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. Eighteen physical therapists are working in the physical therapy section. In the occupational therapy section, five occupational therapists work for the general rehabilitation service and the other four therapists work for the psychiatric rehabilitation. Four acupuncture therapists perform acupuncture and moxbustion. In the Day-care Unit, clinical psychologists and nurses also work. In 2006, speech therapists who had belonged to other departments in the University of Tokyo Hospital were included in our department. From 2009, a speech therapist added to our department, and now three therapists perform therapy for patients with aphasia, dysarthria, and dysphagia.

## Clinical activities

The professor serves as a director of Rehabilitation Center, the University of Tokyo Hospital. The Rehabilitation Center and the Department of Rehabilitation Medicine are united and engage in clinical practice. We have at present no charged ward, and treat about 4,000 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 year students from Wednesday to Friday every week. They experience a few patients and learn how to take a patients' history, physical findings, functional evaluation, and how to plan rehabilitation programs. We have introduced a few of elective students for elective clinical clerkship to our collaborating hospitals with specialized rehabilitation ward.

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

## Research activities

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

1) 3D Motion analysis of patients with musculoskeletal disorders
2) Study on the relationship between sensory deficit and motor control
3) Rehabilitation and long-term outcome in patients with skeletal dysplasias
4) Pathology and treatment for patients with congenital limb deficiencies
5) Analysis of rehabilitation outcome using DPC data

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# Central Supply Service

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## Introduction

Central supply service is an integrated place in the hospital for cleaning and sterilization of previously used devices. All re-usable devices are transported to our division via automated guided vehicle system from surgical center, ward and outpatient clinics. The used instruments are cleaned using standard precautionary procedures, disinfected, reassembled, packaged, and sterilized. The sterilized instruments are then placed at designated sites for use.

One associate professor and one instructor, one nurse, 10 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.

Drying equipment : 5 system drying units.

Sterilizing equipment : 6 autoclaves, 2 ethylene oxide gas sterilizers, 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 (number of containers: 30435 for surgical center, 14201for wards and outpatient clinics in 2015).

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. The number of operations for which the staff re-counted devices was 6651 in 2015.

## 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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**Associate Professor**

Teppei Morikawa, M.D., Ph.D.*

**Lecturer**

Aya Shinozaki-Ushiku, M.D., Ph.D.,

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**Associate**

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Hiroyuki Abe, M.D., Ph.D., Akimasa Hayashi, M.D., Ph.D.,

Atsushi Tanaka, M.D., Ph.D.

Ryu Miyagawa, Ph.D.* (Research, Investigation of Health Hazard by Radiation)

Mariko Tanaka, M.D., Ph.D. * Zen-ichi Tanei, M.D., Ph.D.*

**Clinical Fellow**

Kayoko Ichimura, M.D., Ph.D.,

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## Introduction and Organization

Department of Pathology and Diagnostic Pathology (*) and Division of Diagnostic Pathology of University Hospital have been organized to function as a unit.

We set up Telepathology & Remote Diagnosis Promotion Center (TRDP Center), and started Out-patient Clinic of Pathology. Chief of TRDP Center, Dr. Sasaki explained the detail of cancer pathology to the patients with breast cancer.

To promote the genomic medicine in clinical practice, we set up Center for Genome Pathology Standardization (assisted by Japan Agency for Medical Research and Development) (http://genome-project.jp/). The mission of the Center is to investigate basic technologies for tissue banking, and to hold seminars for doctors and technicians (Drs. Sasaski, Morikawa, Kunita). Clinical Genome Conference started in the University of Tokyo Hospital for the application of cancer clinical sequencing to medical practice (Drs. T and A Ushiku) as a research project of genome medicine (Project organizer: Prof. Hiroyuki Mano).

## Clinical activities (diagnostic pathology and autopsy)

The annual statistics of the pathologic practice in 2016 fiscal year consisted of 17,101 cases of histological examination (23,906 specimens), 17,781 cases of cytology (22,388 specimens), 795 of frozen histology, 391 of intra-operative cytology, 55 cases of autopsy (17.7% of the autopsy rate), and 1 autopsy case from an outside hospital.

The following surgical pathology conferences are regularly held with each clinical division for the cases of various tumors of organs; thoracic organs (Dr. Shinozaki-Ushiku in charge), liver and pancreato-biliary tract (Drs. Ushiku, Hayashi, Tanaka), liver metastasis (Dr. Abe), male genitourinary (Dr. Morikawa) and female genital tracts (Dr. Ikemura), breast (Drs. Ikemura, Sasaki), and bone and soft tissues (Drs. Ushiku, A Tanaka). Biopsy conferences are also held in the cases of kidney (Drs. Shintani, Hayashi), and skin (Dr. M Tanaka).

Our aim in the pathologic practices is to provide the correct diagnosis as soon as possible. We are addressing 'one-day pathology' using a rapid-histoprocessing machinery. We also perform double check for reviewing the reports and slides for all cases of histological examination to prevent a potential misdiagnosis.

Virtual slide scanners have been installed, which enabled us to deposit the biopsy specimens as digital information. We are setting out a future providing system of pathologic images for clinical divisions.

We hold autopsy case conferences on every Monday. Hospital clinico-pathological conferences (CPC)is also held every month as mentioned above, and two cases are discussed in each CPC. The contents are provided as CPC Digest by the hospital internet.

## Teaching activities

The lectures and exercise course of systemic pathology are for the 2nd grade–students. Clinical Clerkship (CC) courses of autopsy and surgical pathology are for the 4th grade students. Four students of 3rd grade took the elective clinical clerkship course.

We instructed all clinical residents (junior course) to submit a report of CPC case as an obligatory requirement of their medical training for each of them. We have made out the digest version of CPC slides open in the hospital (Drs. Shintani and Hayashi), and also started e-learning program for interns to solve the problems in CPC by themselves, thereby facilitating their understanding (Dr. Ikemura).

The Division of Diagnostic Pathology received eight junior residents (total 31 months) in 2016 for their second year program.

## Research activities

Dr. Sasaki is in charge of the research to evaluate feasibility of telepathology for daily practice of diagnostic pathology. We 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 pathological diagnosis by automatic classification of renal biopsy pathology images using Deep Learning Technology (Prof. Kazuhiko Ohe)"

We continue the study to investigate the usefulness of post mortem CT images for hospital autopsy (Drs. Shintani and Abe). We obtain postmortem images with a CT apparatus in the autopsy-assisting CT room, and compare the results with those of autopsy in order to understand the patients' pathophysiology (ref.25, 35 in Department of Pathology and Diagnostic Pathology).

We continue the pathological studies of neoplastic diseases on the basis of surgical pathology conferences (see the pages of Department of Pathology and Diagnostic Pathology). We also cooperate for the projects developing PET and in vivo imaging of cancers of Departments of Upper GI tract Surgery (ref.27 in Department of Pathology and Diagnostic Pathology) and Hepato-biliary & Pancreas Surgery.

Dr. Miyagawa was a Research Associate of Division of Diagnostic Pathology, primarily engaged in Investigation of Health Hazard by Radiation (ref. 17 in Department of Pathology and Diagnostic Pathology).

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See the corresponding section of Department of Pathology and Diagnostic Pathology


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# Department of Corneal Transplantation

**Associate 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 a director (Associate Professor Tomohiko Usui).

## Clinical activities

The clinical activities of this section include corneal transplantation and outpatient clinics for various corneal diseases as a consulting corneal service. The director is 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 and contact lens clinic for special cases are held every Wednesday and Friday. Contact lens clinic for keratoconus and post-keratoplasty is held in the afternoon of Wednesday. At the corneal service, we determine indication for corneal transplantation and follow up patients after the surgery. Total 147 corneal surgeries including keratoplasty were performed in 2016. 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 have pursued to apply regenerative medicine to corneal diseases. In patients with chemical burn of ocular surface, Stevens-Johnson syndrome, and ocular pemphigoid, we try to reconstruct the ocular surface with autologous cultivated limbal, conjunctival and oral epithelial cells. We have established a novel culture technique of limbal, conjunctival and oral epithelial cells and tried a clinical examination with successful results. We are also investigating regenerative medicine of corneal endothelial cells.

In addition, we are investigating the delivery of nucleic acid based drug in corneal neovascularization or corneal dystrophy, gene editing for corneal dystrophy, the expression and function of novel mucin, drug delivery system with soft contact lenses, corneal graft rejection and statistical analysis of long term results in corneal transplantation.

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# Department of Cell Therapy and Transplantation Medicine

**Professor**

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

**Lecturer**

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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 900 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 2016, 17 patients (including 2 children) received autologous HSCT and 28 patients (including 10 children) allogeneic HSCT. We cooperate with the members of Department of Hematology and Oncology, Hematology/Oncology group in the Department of Pediatrics, and Department of Transfusion Medicine.

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

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

Clinical conference for hematopoietic stem cell transplantation: The conference is held monthly. The members of Department of Hematology and Oncology, Hematology/Oncology group in Department of Pediatrics, and Department of Transfusion Medicine join the conference and discuss on HSCT recipients.

## Teaching activities

Together with the members of Department of Hematology and Oncology and Hematology/Oncology group in the Department of Pediatrics, lecture courses on etiology, pathogenesis, clinical and laboratory features, differential diagnosis, therapy and prognosis for all hematological diseases are provided to the second grade medical students. Clinical clerkship courses are given to the third grade medical students, who join the patient care teams consisting of junior and senior medical doctors and learn medical practices and patient management, through playing a role as a junior member of the team, as well as through discussions and presentations.

## Research activities

The major research projects are focused on clinical studies such as development of improved/new methods for hematopoietic stem cell transplantation, immunotherapy for hematopoietic malignancies, and basic studies on hematopoietic stem cells, leukemogenesis and regenerative medicine using hematopoietic cells. In the area of pediatric oncology, we continue the studies on molecular mechanisms of pediatric malignancies such as neuroblastoma, rhabdomyosarcoma, and infant leukemia.

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# Department of Endoscopy and Endoscopic Surgery

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## Introduction and Organization

Department of Endoscopy and Endoscopic Surgery were established in April 1997. Although the present regular staffs of our department are only two doctors, about 80 doctors from other departments including the department of internal medicine, surgery, gynecology and otorhinolaryngology, participate the endoscopic procedures.

## Clinical activities

Endoscopic procedures, including upper gastro-intestinal endoscopy, colonoscopy, bronchoscopy, otorhinolaryngological endoscopy and gynecological endoscopy, are performed from Monday to Friday. Emergency endoscopy is performed in the nighttime or holidays. The numbers of endoscopic procedures in each field are increasing gradually year by year and the total number during 2015 school year reached to 20,000. In the gastrointestinal tract, image enhanced endoscopy for detail inspection and therapeutic endoscopy, including endoscopic submucosal dissection for esophageal, gastric and colorectal tumors, are major advanced fields. 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 outpatient clinic, radiographic procedure rooms, surgery rooms or intensive care units. All endoscopes 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 resident or young doctors in a program of each department.

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

| | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 |
|---|---|---|---|---|---|---|---|---|---|---|
| EGD* | 8796 | 9822 | 10682 | 10556 | 10963 | 11376 | 11840 | 11740 | 11874 | 11944 |
| Colonoscopy | 4360 | 4679 | 4996 | 5152 | 5208 | 5688 | 6000 | 6043 | 6394 | 6814 |
| Bronchoscopy | 201 | 165 | 226 | 255 | 197 | 196 | 169 | 218 | 228 | 362 |
| EUS** | 484 | 402 | 518 | 551 | 630 | 698 | 763 | 766 | 882 | 1084 |
| Enteroscopy | - | 133 | 181 | 311 | 282 | 282 | 375 | 396 | 310 | 86 |
| Laryngoscopy | 91 | 63 | 75 | 70 | 108 | 83 | 128 | 102 | 105 | 125 |
| Colposcopy | 117 | 256 | 307 | 361 | 378 | 365 | 404 | 327 | 295 | 417 |
| Total | 14043 | 15520 | 16566 | 17256 | 17764 | 18688 | 19679 | 19592 | 20088 | 20832 |

*Esophagogastroduodenoscopy, **Endoscopic ultrasonography

## Research activities

Our researches cover a variety of endoscopic fields in cooperation with other departments.

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# Department of Hemodialysis and Apheresis

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## Introduction and Organization

Hemodialysis and related blood purification therapy had been individually performed in their respective departments. However, all the departments' apparatus and human resources were centralized to form the Department of Hemodialysis and Center for Hemodialysis in 2000 at the University Hospital. The Center for Hemodialysis was further renovated and started operations in Fall of 2006. This new Center for Hemodialysis is equipped with one pressure control unit in addition to 12 hemodialysis machines under a state-of-the-art hemodialysis control system. Our concept of a hemodialysis controlling system is a hub to transfer all digital and analog data from patients and to monitor machines, including blood purification machines, to the host computer in our hospital, centralizing all data and administering medical coding and billing robustly. Blood purification machines in the ICU are also connectable to this system, which was developed collaboratively with Nihon Kohden Corp. Blood purification machines are selected uniformly to secure patients' safety while avoiding human error and increasing the overall educational quality of staff members.

## Clinical activities

1. Start of maintenance hemodialysis therapy for end-stage renal disease (ESRD).
2. Regular hemodialysis therapy for hospitalized ESRD patients. Please note that our center does not accept holiday dialysis.
3. Emergency hemodialysis and hemodiafiltration for ICU patients.
4. 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.

## 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. 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 those clinical significance in ICU/CCU.
8. Renal biomarker to determine clinical actionability in CKD and type-2 DN.
9. The potentiality of urine biomarker tests for developing country [JICA-JST: Science and Technology Research Partnership for Sustainable Development].

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# Clinical Research Support Center

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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 whole 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, handling of drugs used in clinical research and assistance with safety information reporting, and clinical research coordination activities. In addition to the existing Consultation Division, the Central Coordinating Unit has added new divisions such as Operation Division, Biostatistics Division, Data Management Division, Monitoring Division and Safety Information Division.

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 I Unit that can conduct Phase 1 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 trials, 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 set up independently from 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 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 conflicts of interest management, 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, to promote and secure safety of regenerative, 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.

We established 3 new divisions outside the unit, education and training division, clinical trial implementation division and university hospital network promotion division. Moreover, in order to strengthen the functions involved widely by the Clinical Research Support Center, we established Education and Training Division, Research Implementation Division and University Hospital Network Promotion Division outside the unit, last year. In the current fiscal year, 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. However, while trying to strengthen the functions, cases of interruption occurred in advanced medical research, revealing lack of cooperation within the Clinical Research Support Center. To prevent the recurrence of such interruptions, we are reviewing our organizational structure aimed at strengthening governance within the center.

As of March 2017, the Center has 9 staff members (1 professor, 1 associate professor, 1 project lecturer, 2 assistant professors, 4 project assistant professor, there are 25 full-time staff members assigned to the Site Coordinating Unit (10 pharmacists, 6 nurses, 3 laboratory technicians, 3 clinical psychologists, 2 project academic support staff and 1 clerical staff. The number of full-time staff assigned to the Central Coordinating Unit is 21. (1 specially appointed staff, 6 pharmacists, 5 laboratory technicians, 4 project academic support staff and 5 clerical staff members. The P I Unit consist of 24 staff members (14 nurses, 2 full-time laboratory technicians, 6 concurrent laboratory technicians 1 project academic support

staff and 1 clerical staff.

## 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). 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 the result we would avoid re-examination of research.

The items processed by the Center as the IRB secretariat in fiscal 2016 included, as for industry-sponsored trials for marketing approval, 41 new protocol applications, 73 study extension applications, 392 protocol amendment applications, 861 SAE/safety information reports, 46 study closure or termination reports. As for investigator-initiated clinical research, the Center processed 25 new protocols, 133 applications for protocol amendment, 78 SAE/safety information reports, and 8 reports for study closure or termination.

Protocol presentations of industry-sponsored trials prior to application to IRB totaled 15 applications. Preliminary consultation and guidance for investigator-initiated research application 27 and 53 applications, respectively.

Clinical Research Support Center managed drug/device inventory for 110 clinical trials (drug 107, devices 3) for regulatory approval, 5 post marketing research, 33 investigator-initiated clinical research, and 10 cases of compassionate use, 2 tissue-engineered medical products in fiscal 2016. The number of prescriptions processed was 957 for research for approval and post marketing research combined, 704 for investigator-initiated clinical research. We managed trial drugs centrally for 6 multicenter research shipped them for 74 times. We masked investigational drugs for 3 double-blind placebo controlled 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. CRCs exclusively involved in investigator-initiated research have been employed as needed. The number of research participants that CRCs interacted with was 5735 in 2016. The number of monitoring visits was 838 in 2016.

As part of patient awareness campaign, we continued updating the Center homepage, 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, 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.

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).

As of fiscal 2016, we have accepted 41 clinical research projects for providing support (28 validation studies and 13 exploratory studies). Eight investigator-initiated clinical trials (which include 2 trials on medical devices, 1 on regenerative medicine, 2 trials as support for other universities) 6 Advanced Medical Care B Programs and 2 trials on regenerative medicine.

With respect to investigator-led trials on medical devices, application for manufacturing and marketing approval was filed with regulatory authorities in November 2014, and was approved on June 18, 2015. Phase I and Phase II clinical trials investigator-initiated trials are near completion.

One investigator-initiated clinical trial in regenerative medicine is currently being conducted.

Besides, 4 clinical trials including investigator-initiated and independent clinical trials to support other facilities are also underway.

**<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 fiscal year 2017, we completed; investigator-initiated phase I study for rare neurodegenerative disease drug, investigator-initiated phase I study for rare pulmonary disease drug, bioequivalence study for a generic drug, and independent study for developing novel medical device. In addition, we are currently conducting a global phase III study in healthy senior volunteers for Alzheimer's disease drug since September 2016.

**<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 University of Tokyo the Institute of Medical Science 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. The system is being used practically by 195 projects as of March 2017. Currently, we are expanding the use of it 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 TR based regional network started in 2014, 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 since 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 trial in order to support and promote clinical trials conducted at the National University Hospitals. Contract templates were created for investigator initiated research and provided to each university hospital by the National University Hospital Council of Japan.

## Education/Training

The Center has been accepting medical students in final year for training course in 'Clinical Clerkship' since it become mandatory in 2013. In addition, we accepted graduate students for 2 day training (enrolled in Master's and Doctoral courses) in the Faculty of Medicine, Graduate School of Pharmaceutical Sciences and the School of Engineering, who took Medical Innovation Initiative course. Medical Innovation Initiative is part of "Fostering Medical Researcher of the Future" project adopted by MEXT (Ministry of Education, Culture, Sports and Technology). Also, we accepted 12 students enrolled in graduate school and Faculty of Pharmaceutical Sciences, both from inside and outside universities. In addition, resident physicians underwent one-month training at the Center, as a part of the M.D. residency-training program.

Education and Training Division was established in 2015 and 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). Currently, 3900 participants are registered for the program.

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 course for national, public and private university hospitals since 2010, commissioned by the Ministry of Education. In June 2016, 5-day training was held under the auspices of the hospital, in which 98 trainees from university hospitals across the country participated.

In addition, we held a joint workshop series with 8 alliance universities in the Kanto Koshinetsu area, (6 organized by the University of Tokyo) which consisted of 5 monitoring workshops, 5 clinical research lecture series. Workshops were attended by 130, 137(45 participants from UTokyo) and 645 (224 from UTokyo) respectively.

In 2016, Japan Agency for Medical Research and Development (AMED) sponsored workshop on "training data managers" was held in Tokyo and Osaka (96 participants at each venue), training workshop for clinical research personnel (1 day, held at the University of Tokyo 46 participated), The University of Tokyo – National University of Singapore joint international symposium on "Human Resources Development" was also held in November 2016.

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 will also be established within the Graduate School of Interdisciplinary Information Studies. Clinical Research Support Center has established system to conduct practical training for course participants.

The Center holds annual "Clinical Research Seminar" in March, nearly 300 people from academia and companies participated last year.

## Research Activities

An endowed course on clinical trial data management was opened in April 2007 with the support of the Center and the Biostatistics Department, Graduate School of Medicine, conducting research and education on data management and biostatistics focused on practical application to research.

As of fiscal 2016, the Center was involved in 18 presentations in scientific meetings, of which 15 were as lead presenters, international conferences 2 (Y. Uemura). The Japan Society of Clinical Pharmacology and Therapeutics 6 (A. Okuma, M. Takata, S. Tanaka, Takeda, Y. Uemura, Y.Omori), Conference on CRC and Clinical Research 3 (N.Ogura, A.Nagamatsu, A.Kishi) Japan Society of Clinical Trials and Research 2 (S.Karasawa, S.Nogawa) other presentations 2 (T.Yamazaki, A. Kishi ) 13 lectures (T.Yamazaki, M. Takata, A Kishi), 31 publications and academic papers etc. (English papers 19, Japanese papers 0, review papers 9 and 3 Japanese books)

## Publications


1) Ueshima K., Itoh H., Kanazawa N., Komuro I., Nagai R., Takeuchi M.,and Yamazaki T., for the EMPATHY study group: Rationale and Design of the Standard Versus Intensive Statin Therapy for Hypercholesterolemic Patients with Diabetic Retinopathy (EMPATHY) Study: a Randomized Controlled Trial. J Atheroscler Thromb 23:976-990,2016
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# University Hospital Medical Information Network (UMIN) Center

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## Introduction and Organization

The University hospital Medical Information Network (UMIN) (the original name was the University Medical Information Network), was established in 1989. While general-use computer systems were implemented at all national university hospitals around the end of the Showa era (late 1980s), Dr. Shigekoto Kaihara, chair and professor at the Hospital Computer Center, University of Tokyo Hospital, led a project to connect these computer systems in a network in order to share information for better communication. Finally, the Ministry of Education, Culture, Sports, Science and Technology approved a budget to initiate the UMIN Center. The UMIN Center was founded within the Hospital Computer Center, University of Tokyo Hospital, and was officially opened in March 1989. Dr. Tsunetaro Sakurai became an associate professor as the first full-time UMIN staff. The following are the objectives of the UMIN Center, as initially outlined in 1989 (No.6 was added later):

1. Provide up-to-date information for healthcare professionals
2. Promote digitalized communication among healthcare professionals
3. Support collaborative projects among university hospitals
4. Support collaborative medical research
5. Standardize data format and support data collection
6. Support medical education and clinical training

The original UMIN system utilized an N1 protocol, which was developed in Japan and was the only solution at the time to connect general-use computers of the five major computer vendors in Japan, although it was poor in function, supporting only line-mode, character-based terminals.

In 1994, we launched a service through the Internet, and it began to spread in those days. The number of UMIN users gradually increased, mainly in the E-mail service.

In 1996, Dr. Takahiro Kiuchi took up a new post while

Dr. Sakurai was promoted to professor at Hokkaido University. Dr, Kiuchi updated the system to be web-based. With the rapid spread of the Internet in Japan, UMIN users dramatically increased.

The UMIN Center subsequently started to provide three major information services: (1) the ELBIS (Electronic Library for Biomedical Sciences) as of 1997, (2) the INDICE (Internet Data and Information Center of Clinical Research) as of 2000, and (3) the EPOC (Evaluation System of Postgraduate Clinical Training) as of 2004.

In April 2002, the UMIN Center became an independent entity, with the adjusted name of University Hospital Medical Information Network Center, as per an internal arrangement at the University of Tokyo Hospital. In 2003, a budget for a new professor position was officially approved by the Ministry of Education, Culture, Sports, Science and Technology. Then, Dr. Kiuchi was promoted to become the first professor of the UMIN Center on April 1, 2004. The UMIN Center became part of the Faculty of Medicine, as the Department of Health Communication, School of Public Health, which was established in April 2007.

## Clinical Activities

Although the UMIN Center is one of the central medical examination and treatment institutions of the University of Tokyo Hospital, the center does not provide direct patient care services, but provides services for medical researchers and practitioners throughout Japan. We currently have about 440,000 registrants, and approximately 110,000,000 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
- Drug information text database for pharmacists
- Drug information text database for patients
- 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. 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. Until today, more than 570 cases of living donor liver transplantation and 25 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, lung transplantation, and deceased donor liver transplantation. So far 84 heart transplantations and 7 lung transplantations have been performed.

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# Center for Epidemiology and Preventive Medicine

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## Introduction and Organization

Following the inauguration of a new Central Clinical Service Building (Central Care 2) in November 2006 (Heisei 18) in the University of Tokyo Hospital, the Center for Epidemiology and Preventive Medicine was established on January 1, 2007, within the Central Clinical Facilities and the relevant regulations were revised. On January 9, the Working Group for the Establishment of the Center for Epidemiology and Preventive Medicine was organized; on April 1, Steering Committee for the Establishment of the Center for Epidemiology and Preventive Medicine was organized; preparation for offering its services continued until May 31; on June 4, 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) by doing the above 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 the above 1), 2) and 3) into practice.

In the administrative organization of the Center for Epidemiology and Preventive Medicine, its Director directly under the Director of the Hospital is responsible for the entire organization. The management of the Department is also supported by the Department of Clinical Epidemiology and Systems and the Department of Ubiquitous Preventive Medicine. In addition, 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 five Clinical Divisions (Breast and Endocrine Surgery, Gynecologic Surgery, Ophthalmology and Vision Collection, Oral-Maxillofacial Surgery, Dentistry and Orthodontics, and Neurology).

The staff of the Center for Epidemiology and Preventive Medicine is composed of nine physicians (four regular physicians and five physicians from the related departments). One of the regular physicians also performs upper gastrointestinal endoscopy and colonoscopy in the Department of Endoscopy and Endoscopic Surgery. Our department also has five regular nurses and five regular secretaries. When our department was established, the number of staff was increased in other divisions. Among our staff, one nurse (full-time), three radiological technologists (full-time) and three medical technologists (full-time) are assigned respectively to the Department of Endoscopy and Endoscopic Surgery, the Radiological Center and the Clinical Laboratory Center.

## Clinical activities

In addition to basic examinations which are open to the public, our department provides these eleven options: 1) comprehensive cardiovascular examinations, 2) home blood pressure screening, 3) comprehensive cerebrovascular examinations, 4) check up dementia, 5) colorectal cancer screening, 6) uterine cancer screening, 7) breast cancer screening, 8) lung cancer screening, 9) tumor marker diagnosis, 10) estimation of gastric cancer risk, and 11) oral/dental examinations. While meeting the needs of examinees, we have increased the number of the optional examinations and provided higher levels of examinations.

The physicians of our department are responsible for analyzing the results of examinations and screenings, performing overall evaluations, and consultations with examinees. One of our important services is that we take approximately 30 minutes per examinee to perform comprehensive medical examinations. Formally, the examinee is notified in writing of the results within approximately three weeks after the examination. We also offer each examinee a free 20-minute consultation so that we can help him/her understand the results or decide whether or not to have further work-up.

## Teaching activities

Although our department has no students directly under our supervision being a clinical service, we offer education in epidemiology to graduate students in the Department of Clinical Epidemiology and Systems and the Department of Ubiquitous Preventive Medicine.

## 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. In 2007, the first year of our department, we collected data on examinees and designed a pilot database. From 2008 onward, we continue to collect data and conduct their cross-sectional and longitudinal analysis.

## Past activities

In the fiscal year (FY) 2016from April 1, to March 31, 2017, the total number of examinees (who had basic examinations and optional examinations) was 7,610, including 2,803 in basic examinations, 544 in complete cardiovascular examinations, 4 in home blood pressure screening, 688 in complete cerebrovascular examinations, 89 in check up dementia, 346 in colorectal cancer screening, 545 in uterine cancer screening, 676 in breast cancer screening, 586 in lung cancer screening, 1,060 in tumor marker diagnosis, 225 in estimation of gastric cancer risk, 18 in upper gastrointestinal endoscopy (later), and 46 in oral/dental examinations.

When examinees visit other departments in our hospital for a work-up or treatment, we write a letter of referral by request. In the FY 2016, we issued 769 letters of referral to other departments in our hospital and 35 to other hospitals.

We have expanded our public relations efforts and during the FY 2016 15,000 brochure were delivered.

We also prepared posters which were placed within our hospital and on the campus of the University of Tokyo as well. Our homepage (the above URL) has been constantly updated to provide the latest information for examinees.

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1. Subclinical carotid atherosclerosis associates with impairment in immediate memory
   Lumine Matsumoto 1)2), Kazushi Suzuki 1)2), Yoshiko Mizuno 2),Yumiko Ohike 2), Atsuko Ozeki 2) ,Satoshi Ono 2), Mikio Takanashi 2), Daigo Sawaki 2), Toru Suzuki 2), Tsutomu Yamazaki 2), Shoji Tsuji 1), Atsushi Iwata 1),3)
   1) Department of Neurology, The University of Tokyo
   2) Center for Epidemiology and Preventive Medicine, The University of Tokyo
   3) Japan Science and Technology Agency, PRESTO
   The 68th Annual Meeting of the American Academy of Neurology April 15- April 21, 2016 Vancouver, BC
2. Efficacy of non-exposed endoscopic wall-inversion surgery (NEWS) as an advanced method of full-thickness resection for gastric tumor; Keiko Niimi, Takashi Mitsui, Susumu Aikou , Sinya Kodashima, Nobutake Yamamichi , Hiroharu Yamashita, Mitsuhiro Fujishiro, Yasuyuki Seto, Kazuhiko Koike, UEGW 2016/10/19 (Vienna, Austria)
3. American Heart Association Scientific Sessions 2016 (November 12-16 2016, New Orleans, USA)
   Mikio Takanashi, Satoru Takase, Yoshino Taira, Takeshi Kimura, Sachiko Okazaki, Pengfei Xu, Chengcheng Li, Futoshi Shionoiri, Yoko IIzuka, Jun-ichi Osuga, Shun Ishibashi, Takashi Kadowaki, Hiroaki Okazaki
   “Amelioration of streptozotocin-induced diabetic hypertriglyceridemia in the absence of hormone-sensitive lipase”

# Division of Tissue Engineering

**Director & Professor**

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**Homepage http:// square.umin.ac.jp/t-e/**

## Introduction and Organization

Division of Tissue Engineering was established as a special medical office in The University of Tokyo Hospital, in October 2001 and has a fully equipped 800 $m^2$ laboratory on the 8th floor of the In-patient Ward B. Division of Tissue Engineering consists of Department of Bone & Cartilage Regenerative Medicine, Department of Vascular Regeneration, Department of Advanced Nephrology & Regenerative Medicine, Department of Cartilage & Bone Regeneration, Project for Regeneration Medicine of Hematopoiesis, Corneal Tissue Regeneration Project, and Laboratory for Pediatric Regenerative Medicine. We have invited talented personnel of various fields from home and abroad. One project associate professor and one or two project research associates who are assigned to each department are conducting research with many post graduate students. Aiming at clinical application within a few years, 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 Regenerativen 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.

## Research activities

As for bone and cartilage regeneration, we aim to develop easy, precise, non-invasive systems to detect osteoblastic and chondrocytic differentiation, to determine a finite set of signaling factors sufficient for induction of osteoblasts and chondrocytes, to develop a cell-sheet culture system for bone and cartilage, to devise a method to induce osteogenesis and angiogenesis simultaneously, to screen for compounds that induce bone and cartilage regeneration, to develop non-viral gene transfer methods by nano-micelle technology and to generate, to devise methods to precisely control 3D shape of biomaterials, and to transplant regenerated bone and cartilage. To achieve these goals, we are conducting research on bone and cartilage biology, developmental biology, stem cell biology and regenerative medicine. Regarding the clinical study “Development of implant-type tissue-engineered cartilage for patients with nasal deformity in cleft lip and palate”, which was authorized to of conduct on Mar 18th 2011, we have completed the transplantation on 3 patients as had been planned. The outcomes have been good so far with no major complications.

As for renal regeneration, we aim at specific method to differentiate human iPS cells to kidney cells. We also try to clarify the epigenetic regulation of BMP7. To achieve these goals, we are conducting epigenetic analysis of human kidney derived iPS cells. Moreover, we are trying to establish 3-D culture system for safe clinical application of human iPS cells, and determining new target of cancer therapy by comprehensive epigenetic analysis of cancer dereived iPS cells.

In the department donated by FUJISOFT ABC, 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”.

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.

**Basic Research on human ES cells**

Besides, to promote basic research on human embryonic stem cells with our eyes set on applications in the future, Department of Clinical Renal Regeneration is carrying forward the application procedures to obtain human ES cells from Institute for Frontier Medical Sciences, Kyoto University, which will be approved shortly.

## 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” have been 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. Department of Plastic Surgery is conducting research using this facility.

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# Department of Clinical Research Governance

**Director & Project Professor**

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**Homepage http://www.h.u-tokyo.ac.jp/english/centers-services/organization/**

## History and Overview of the Organization

The Department of Clinical Research Governance was established independently from the Clinical Research Support Center on January 1, 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 composed of three offices: 1) Office of TR Strategy Promotion, 2) Office for Clinical Research Education, and 3) Office of Clinical Quality Assurance & Compliance. These offices mutually cooperate to promote and strengthen governance functions within the hospital.

The following activities are carried out by the Office of TR Strategy 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) examinating 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 for Clinical Research Education are as follows: (1) educational activities for clinical researchers; and (2) the dissemination of workshop summaries.

The activities of the Office of Clinical Quality Assurance & Compliance are as follows: (1) quality assurance-related activities, such as the auditing of clinical trials and clinical studies and administrative structure/system audits as well as improvement proposals; (2) proposals related to the establishment of a quality assurance system; (3) reliability-related guidance, advice and consultation; (4) support for responding to compliance reviews, etc., for clinical trials and clinical studies conducted by the University of Tokyo Hospital, as well as the centralized

management of results; (5) the centralized management of audit results; and (6) confirmation of the implementation of corrective and preventive measures based on audit/inspection findings.

The Department of Clinical Research Governance consists of one manager (a full-time post from August, 2015) and two staff members of the Office of TR Strategy Promotion (one special researcher/URA and one clerical staff [temporary]), as of March 2017. The Office for Clinical Research Education consists of one member (one research associate). The Office of Clinical Quality Assurance consists of one head (project senior specialist) and two staff members (a project specialist and a project academic support staff) .

## Medical Care and Activities

The Office of TR Strategy Promotion has undertaken the following activities.
1) Organization coordination activities: assisting the Special Clinical Research Steering Committee, assisting the Special Clinical Research Checkup Committee, assisting with the assembly of a structure for a regenerative therapy provision plan, and assisting the preparation of reports on clinical research activities at core hospitals under the Medical Service Law (approved on March 25, 2016) and for surveys conducted by the Ministry of Health, Labour and Welfare.
2) Activities related to TR Promotion: adopting the role of administrative headquarters when applying for Projects of Translational and Clinical Research Core Centers, hosting medical-engineering collaborative meetings (cooperation with Ota-ku), and organizing the meeting to exchange opinions with the president of AMED.
3) Intellectual property-related activities: evaluation of intellectual properties for network programs for accelerating the work of bridging research, organizing two seminars for intellectual properties, and conducting 10 consultations regarding intellectual properties (10 patent cases).
4) Others: reviews of application forms for Grants-in-Aid for Scientific Research and for the University of Tokyo Research Grant, investigations of research paper publication activities, hosting of the “Forum for Development of Seeds for Advanced Medicine, 2017” (administrative office), and support for the Center of Innovation Program of the University of Tokyo (support for departmental cooperation, support for holding one symposium, and support for holding two seminars).

The Office of Clinical Quality Assurance & Compliance was newly established in April 2015 and has undertaken the following quality assurance activities.
1) Quality assurance-related activities:1. Regarding 3 investigator-initiated clinical trials at the University of Tokyo Hospital, a total of 6 cases were audited. Regarding 2 investigator-initiated clinical trials (a multi-center clinical trial and a trial for a medical device) at other university hospitals, 2 cases were audited. 2. Regarding clinical research, 1 case of clinical research at other university hospitals was audited. Regarding clinical research at the University of Tokyo Hospital, 2 cases of advanced medical care B were audited and the audit procedures and protocols for 2 clinical studies were prepared. The members of the office explained the audit schedule and contents, etc. Preparations for other audits have also been initiated. 3. When research funding was secured, the audit was entrusted to the external audit organization under supervision by the Office.
2) Support for responses to various inspections: Regarding surveys for TR centers, AMED, and clinical research core hospitals, the members attended and explained the structure for quality assurance. The members also attended the inspections performed by the FDA.
3) Educational activities:1. For a “Lecture Series” conducted by the clinical research support center, the office was involved in making programs, inviting lecturers, and conducting the seminar. 2. Supervisions of quality assurance were conducted for members of the clinical research support center.
4) Other activities:1. Regarding the activities of the UCHT Alliance, mutual visits among 8 university hospitals were conducted and the structure for quality assurance was evaluated. 2. For the National University Hospital Clinical Research Promotion Initiative (NUH-CRPI), a member joined and led the

discussion on quality assurance. 3. The members attended the Japan Society of Quality Assurance and the Annual Scientific Meeting of the Japanese Society of Clinical Pharmacology and Therapeutics, and an analysis of audit results was reported.

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# Department of Child Psychiatry

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## Introduction and Organization

The Department of Child Psychiatry was established in April 2005 as the clinical counterpart to the Clinical Education Center of Mental Development, both of which are funded by the special grant for faculty development. The major aim of the Clinical Education Center is to train mental health specialists in various fields with a fundamental grounding in child psychiatry and neurosciences. Much of the services provided are based on the 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 multi-disciplinary 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, 3 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 2016, the Department of Child Psychiatry consisted of 14 psychiatrists and 7 psychologists (full-time and part-time). 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), Mental Retardation (MR), tic disorders and child & adolescent Obsessive-Compulsive Disorders (OCD).

Number of new patients in 2016 was 251 and slightly larger than that in 2015. A large part of the new patients consisted of patients with ASD, ADHD or tic disorders. Out of 251 patients, children of elementary school age were 111, and children of junior high school age were 41. In other words, children of elementary or junior high school age were about two-thirds of the patients. Number of preschool children was 64, and about twice of that in 2015, suggesting an increase in 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 October 2016, and about 160 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.

Effectiveness of a program of group cognitive behavior therapy for adults with high-functioning ASD the revised program is investigated in a

randomized control trial.

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.

Comprehensive Behavioral Intervention for Tics (CBIT) is provided for children and adolescents with Tourette syndrome, and preliminary study of its effectiveness is undertaken.

We started 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 and assisted reproduction technologies on emergence of ASD. We are analyzing samples of individuals from a multiplex family of ASD by exome sequencing also. We are collecting and analyzing DNA samples of patients with Tourette syndrome and their parents also.

**Neuroimaging**

Studies include structural MRI, Near-Infrared Spectroscopy (NIRS) and functional MRI with exploring the pathogenesis of developmental disorders such as ASD. One of the intensive study is the examination of prefrontal blood flow in ASD and ADHD by NIRS which is non invasive and easily applicable to children and developmentally disabled individuals. Possibility of NIRS as a predictor of efficacy of methylphenidate for children with ADHD is intensively examined also. Functional MRI study of adults with ADHD and adults with Tourette syndrome by delayed reward task is in process.

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# Department of Pain and Palliative Medicine

**Homepage http://www.h.u-tokyo.ac.jp/patient/depts/pailiative/**

## 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 2016, the number achieved to more than total 900 cases. To date we have become to collaborate with almost all departments treating cancer in our hospital. These results indicate that the hospital understands the significance of palliative care well and relies on our team.

## Education

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

1) Palliative care training program

The training course (selection) for two months ( or * for one month )

・ Program to acquire basic knowledge and practice of palliative care for targeting all junior residents. * Only in "Comprehensive Internal Medicine" selection.

**The training course (selection) for four or eight months**

・ Program to acquire basic knowledge, practice, and skills of communication for doctors who need to be clinical oncologists or pain and palliative care specialists.

2) Curriculum

**Contents of training**

・ All junior residents are assigned to the pain and palliative care team. They chiefly participate in palliative care practice as a member of the team.

・ In the course for four and eight months, they learn to make palliative care plans for inpatients, discuss palliative care of the cases with patients' attending doctors, ward staff, and execute these palliative care plans.

**Goal to attain**

・ Palliative care for inpatients (around 40 cases a day): They acquire the outline of control of physical and psychiatric symptoms of the patients with common diseases in our country such as digestive cancers. They also learn the outline of spiritual and family care.

・ Cancer registry: In The University of Tokyo Hospital, it is not unusual that the patient whom the pain and palliative care team treats is often in an end stage, and his or her condition changes physically and mentally day by day. Residents should input the clinical data about palliative care of such patients concisely to the database. They acquire the outline of data management of the palliative care connected directly to a clinical research.

・ Communicative competence: The clinician often has to break "Bad news" to his patients time after time along the course of their illness. It is very difficult for the clinician to provide the appropriate information about diagnoses, recurrence, progression and prognosis of illness to his patients. The oncologist has to deal with patients' strong grief and feeling of loss when their illness is obviously progressive as well as has to manage both their accepting realities and expecting hopes. We practice according to the guidelines of communication that is recommended by the Japanese Psycho-Oncology Society.

Educational

・ In the intensive course for the first-year residents, we prepare lectures about:
  # pain management
  # diagnoses and management of delirium
  # Introduction of guidelines in the field of palliative medicine and their use
  # Basic medication for palliative care
  # Spirituality and whole person care for Japanese patients facing death

**Daily and weekly schedule**

・ Conference: Monday-Friday (every weekday); 9:00-10:30am

・ Consultation: Monday-Friday (every weekday); from the end of morning conference, up to the completion of all the requested consulting of the day.

・ The cancer registry: They input data in the ward round with the HIS (Hospital information system) terminal on each floor.

**The instruction system**

・ Inpatient care: Residents participate in the consultation team (pain and palliative care team) that contains medical instructors. We pain and palliative care team take charge of about 40-50 inpatients usually.

・ Multidisciplinary conference: Psychiatrists, pain clinicians/Anesthesiologists, orthopaedicians, pharmacists, medical social workers and others participate in the daily or weekly conference besides the regular member of the pain and palliative care team. Residents can discuss actively the multidisciplinary palliative care plans which our team should carry out. Participants from each occupation also guide the care plans from their viewpoints of experts.

## Research

The clinical information accumulated from the palliative care consultation is input to the concise database simultaneously and utilized for various kinds of clinical researches to submit to the international medical journal such as "International Journal of Radiation Oncology Biology Physics", "Journal of Pain and Symptom Management" and so on.

To date, we the Department of Palliative Medicine have contributed to the progress of following fields of investigations. Please refer to our homepage for results in details and acquisition of the research fund.

1) Evaluation and quality assurance of special pain and palliative care team
2) Cancer Survivorship
3) Investigating cognitive dysfunction induced by pain
4) Cancer treatments-induced neurological side effect
5) Synergistic influence between sleep disorder and pain
6) Assessment of neuropathic pain
7) Relationships among our university hospital and local hospitals and clinics
8) Palliative care supporting metastatic breast cancer patient
9) In palliative medicine field, clinical researches and questionnaires

## Publications


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2. Sumitani M, Ogata T, Natori A, Hozumi J, Shimojo N, Kida K, Yamauchi H, Yamauchi T. Poor efficacy of the phosphorylated high-molecular-weight neurofilament heavy subunit, a biomarker of axonal damage, as a marker of chemotherapy-induced peripheral neuropathy. BioMed Rep 2016; 4: 758-60
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(And, more than 27 Japanese articles)

# Department of Cancer Resource Center

**Chief**

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

**Associate chief**

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

**Counseling staff**

Nobuko Yamaji, RN., Megumi Yasuda, RN.

**Homepage http://www.h.u-tokyo.ac.jp/patient/depts/cancer_support/**

## 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, in order to select the best treatment for oneself from among the therapies presented by doctors, the person needs to accurately understand the doctors' explanations. 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, and nursing services. The Cancer Counseling and Support Center provides patients with advice and support so that they can resolve such 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.

**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-4pm weekdays (except 12 noon-1pm). Our center provide advices for nothing.

## Research activities

Our research field covers the relation between appearance changes caused by cancer therapy and Patients' quality of life.

## References and Presentation

1. Takako W. Benefits of cover makeup for survivors. Journal of Clinical Oncology 34, no. 26_suppl (October 2016) 259-259. http://ascopubs.org/doi/abs/10.1200/jco.2016.34.26_suppl.259
2. Takako W. Benefits of cover makeup for survivors. Palliative care in oncology Symposium
3. Takako W. Appearance care service in The University of Tokyo Hospital. The 54th Annual Meeting of Japan Society of Clinical Oncology (JSCO)

# Department of Genome Informatics

**Director & Professor**

Takashi Kadowaki, M.D., Ph.D.

## 1. Organization

The Department of Genome Informatics started as a special unit conducting research on human genetics and clinical epidemiology in 2003. Our section functions as the unit to establish clinical and epidemiological data sampling/ management and to accomplish an appropriate and efficient application of results of recently advanced human genetics and genomics. In addition, the unit contributes to training and educating specialists of clinical epidemiology and human genetics. Our section also supported designing of clinical / genetic studies. It consists of one professor and different specialties participating in the department. They include cardiologists, diabetologists, and epidemiologists.

## 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 35,000 cases and more than 54,000 controls. We also found that one gene was associated with diabetic nephropathy and two genes were associated with diabetic retinopathy.

We conducted whole genome sequence and analyzed the sequence data of the subjects with type 2 diabetes in collaboration with RIKEN and BioBank Japan. We are exploring the genetic and environmental factors by selecting case and control from BioBank Japan for genome-wide analysis concerning deterioration of diabetes and diabetic complications (diabetic nephropathy and diabetic retinopathy). 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.

The insulin receptor gene mutations were analyzed in four patients with severe insulin resistance 1). Using online databases, we analyzed insulin receptor gene missense mutations and demonstrated that mutations causing Donohue syndrome were more frequently located in the fibronectin type III domain (FnIII) than those causing the milder insulin resistance. We revealed that the mutant insulin receptor genes in the FnIII reduced insulin proreceptor processing, by functional analysis using cultured cells. In silico structural analysis revealed that missense mutations predicted to severely impair hydrophobic core formation and stability of the FnIII domains. These results suggest the importance of the FnIII domains, provide insight into the molecular mechanism of severe insulin resistance, and will aid early diagnosis.

In cardiology and vascular medicine, we focused on atherosclerotic diseases such as coronary stenosis and myocardial infarction. It is important to accumulate and analyze data obtained in practice and genetic data to gain insight into a clinical picture. Analyzing data collected provide detailed genetic factors of the coronary atherosclerotic diseases and

their clinical outcome.

## 3. References

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# Department of Clinical Genomics, Medical Genome Center

**Director & Professor**

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

## Organization

The Department of Clinical Genomics started as a special unit conducting genomic medicine or clinical human genetics services in 2003. Our department functions as the core unit to accomplish an appropriate and efficient application of results of recently advanced human genetics and genomics to clinical practice in the hospital and as the unit of training and educating specialists of human genetics practice. It consists of one professor and many different specialties participate in the department. They include pediatricians, obstetricians, internist (cardiologists, diabetologists, and neurologists), surgeons, and staffs of the Departments of Clinical Laboratory Medicine, Human Genetics and Nursing Science.

## Activities

The exclusive consultation room (Room 200) is allocated in the outpatient clinic. Consultation and counseling is performed by a team of medical doctor and non-M.D. staffs. All cases are reviewed and discussed at the conference which is held on the 1st Monday every month. Counseling of participants in researches including genome or gene analysis is a duty with which the hospital and the faculty charge the department. To build suitable clinical systems including modern genomic medicine we are cooperating with other departments. We are participating in Marfan's Syndrome Clinic which is managed collaboratively by the Departments of Cardiovascular Surgery, Cardiovascular Medicine, Pediatrics, Spinal Surgery and Ophthalmology.In collaboration with Clinical Laboratory Center, Pharmaceutical Services, Departments of Planning Information and Management, and several clinical departments, pharmacogenetics tests including those for proton inhibitor, warfarin, irinotecan, and tacrolimus, are conducted.

## Publications

1. Ichinose Y, Koh K, Fukumoto M, Yamashiro N, Kobayashi F, Miwa M, Nagasaka T, Shindo K, Ishiura H, Tsuji S, Takiyama DY. Exome sequencing reveals a novel missense mutation in the KIAA0196 gene in a Japanese patient with SPG8. ***Clin Neurol Neurosurg.*** 2016 May;144: 36-8.
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4. Amiya E, Morita H, Hatano M, Nitta D, Hosoya Y, Maki H, Motozawa Y, Sato N, Ishiura H, Numakura S, Shintani Y, Kinugawa K, Takeda N, Shimizu J, Tsuji S, Komuro I. Fukutin gene mutations that cause left ventricular non-compaction. ***Int J Cardiol.*** 2016 Nov 1;222:727-9.
5. Udagawa T, Jo T, Yanagihara T, Shimizu A,

Mitsui J, Tsuji S, Morishita S, Onai R, Miura K, Kanda S, Kajiho Y, Tsurumi H, Oka A, Hattori M, Harita Y. Altered expression of Crb2 in podocytes expands a variation of CRB2 mutations in steroid-resistant nephrotic syndrome. ***Pediatr Nephrol.*** 2017 May;32(5):801-809.

6. Matsukawa T, Koshi KM, Mitsui J, Bannai T, Kawabe M, Ishiura H, Terao Y, Shimizu J, Murayama K, Yoshimura J, Doi K, Morishita S, Tsuji S, Goto J. Slowly progressive d-bifunctional protein deficiency with survival to adulthood diagnosed by whole-exome sequencing. ***J Neurol Sci.*** 2017 Jan 15;372:6-10.

# Department of Genome Analysis, Medical Genome Center

**Director and Professor**

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

The Department of Genome Analysis started as a core facility at the University of Tokyo Hospital in 2011. Next generation sequencers (NGSs), which have been installed until now, include three Illumina HiSeq2500s, one Pacific Biosciences RS II, Oxford Nanopore MinION system, and one Illumina MiSeq. Robotics for preparation of samples has also been installed. Computer servers for processing of massive amount of genome data have been installed in the server room, which are connected to NGs via network system isolated from the internet.

## Activities

The core facility offers genome sequencing employing NGSs for other laboratories in the University of Tokyo Hospital as well as for the in-house projects. The core facility further offers genome sequencing employing NGSs for laboratories outside of the University of Tokyo. Approximately 2,000 samples per year have been analyzed.

## Research Accomplishments

Collaborative researches have achieved multiple accomplishments including identification of the causative gene for autosomal recessive Charcot-Marie-Tooth disease (MME), familial amyotrophic lateral sclerosis (CCNF), and progressive neuro-degenerative encephalopathy with atypical infantile spinal muscular atrophy (TBCD), development of a reference database of genetic variations in the Japanese population, and case reports of SPG8 and tubular aggregate myopathy.

## Publications

1. Nishikawa A, Mori-Yoshimura M, Segawa K, Hayashi YK, Takahashi T, Saito Y, Nonaka I, Krahn M, Levy N, Shimizu J, Mitsui J, Kimura E, Goto J, Yonemoto N, Aoki M, Nishino I, Oya Y, Murata M. Respiratory and cardiac function in japanese patients with dysferlinopathy. ***Muscle Nerve.*** 2016 Mar;53(3):394-401.
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# Cooperative Unit of Medicine and Engineering Research

**Organization**

The University of Tokyo Hospital
Cardiovascular Medicine, Nutrition and Metabolism, Surgical Oncology, Vascular Surgery, Artificial Organ and Transplantation, Cardiac Surgery, Thoracic Surgery, Neurosurgery, Urology, Orthopaedic Surgery, Oral and maxillofacial Surgery, Radiology, Tissue Engineering Unit, Department of Clinical Epidemiology & Systems, Bone & Cartilage Regenerative Medicine, Cartilage of Bone Regeneration, Department of Immunotherapeutics (Medinet), Division of Science for Joint Reconstruction

**Engineering and Pharmaceutical Research**

Chemical System Engineering, Mechanical Engineering, Precision Engineering, Quantum Engineering and System Science, Nuclear Engineering and Management, Chemistry and Biotechnology, Material Engineering, Information Science and Technology, Frontier Sciences, Pharmaceutical Sciences Laboratory of Chemistry and Biology, Center for Disease Biology and Integrative Medicine, Center for Disease Biology and Integrative Medicine Regenerative Medical Engineering, Center for Disease Biology and Integrative Medicine Clinical Biotechnology, Research Center for Advanced Science and Technology, Institute of Industrial Science

**Homepage http://plaza.umin.ac.jp/~ikourenk/**

## 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$^2$ that is consisted

of a portion of the first floor and the basement of an administration building came to a decision by the conference.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

## 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 analysed 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.

**Laboratory of Nano-crystals in Oncology**

*Department of Chemical System Engineering*

*Department of Surgical Oncology*

To develop an exact diagnosis and treatment system for the micro-metastasis of neoplasm by using nano-crystal particles, and to introduce it to clinical use. To visualize peritoneum metastases (peritonitis) and micro-metastasis of neoplasm which cannot be checked in naked eye, and apply it to an operation or the determination of a medical treatment plan. To search for the new method for treating neoplasm by using biological changes of the cells after up taking nano-crystal particles.

**Research and development of micro-neurosurgical robotic systems**

*Department of Neurosurgery, The University of Tokyo Hospital*

*Mitsuishi-Sugita Laboratory, Department of*

*Mechanical Engineering, School of Engineering*
Development of micro-neurosurgical robotic systems and advanced microscopic image processing for automated 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, they consist of establishment of personalized medicine as translational research, selection of drug targets by proteomics, interpretation of transcriptional regulations and drug development by targeting transcription factors in cardiovascular diseases (arteriosclerosis, cardiac hypertrophy, cardiac failure, etc.). Other analyses and development are also quite active, such as creation of transgenic animals, analyses of genomic functions, clinical safety monitoring by clinical database and assessments of clinical information systems.

**Development of diagnostic system of orthopedic biomechanics**
*The Department of Orthopaedic Surgery, The University of Tokyo.*
*Graduate School of Information Science and Technology, The University of Tokyo.*
To develop a non-invasive method for predicting bone strength by finite element method analysis. Newly administration of Teriparatide to the rheumatoid patients and analyses of its effects by finite element method with bone metabolic markers, bone density, and computed tomography.

**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 (BNCT) using small neutron accelerator equipped to hospital and also aim to augment cancer therapy combined with immunotherapeutic approaches.

**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*
*Laboratory of Regenerative Medical Engineering, 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 deseases by Applied Metabolic Biotechnology**

*Department of Cardiovascular Medicine, Graduate School of Medicine*
*Department of 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 chondrocytic 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" nano-particles 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.

**Intervention study of exercise therapy for patients with gluteal claudication after abdominal aortic or iliac arterial surgery.**

*Mechano-Informatics, Graduate School of Information Science and Technology, The University of Tolyo*

*Department of Vascular Surgery, Faculty of Medicine, The University of Tokyo*

After minimally invasive endovascular aortic and iliac repair for aneurysm with stent grafts and coil embolization, we apply intervention with exercise therapy in case of postoperative gluteal claudication. We aim to explore the mechanism of improving gluteal claudication and establish the optimal exercise therapy, by analyzing the biomechanical motion of walking with motion capture method before and after the exercise therapy.

**Analysis of the role of nitric oxide in the mechanisms of renal and vascular injuries by the probes for active oxygen and nitric oxide.**

*Department of Cardiovascular Medicine*

*Laboratory of Chemistry and Biology, Graduate School of Pharmaceutical Sciences*

It has been elucidated that the oxidative stress and nitric oxide have injurious and protective roles for renal and vascular dysfunction, respectively. However, it is difficult to detect them correctly in cells because they are unstable. We aim to develop the way to detect active oxygen and nitric oxide by using the in vivo and in vitro models of renal and vascular dysfunction.

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# Department of Disaster Medical Management

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## Introduction and Organization

Responding to the Great East Japan Earthquake in 2011, the University of Tokyo Hospital has decided to set out to establish "disaster medical management studies" in terms of need not only to provide medical treatment at the time of disaster but also to develop a new academic field that provides bird's-eye view on overall disaster medicine. In March 2012, we made an announcement to establish "Department of Disaster Medical Management" in the Public Comment.

In July 2012, Associate Professor Dr. Hiroyuki Nakao was assigned the post as the first General Manager of the Department of Disaster Medical Management. Afterwards, in January 2015, Professor Dr. Tadashi Iwanaka, the Hospital Vice Director, was assigned the post as the second General Manager. In April 2015, Professor Dr. Masaomi Nangaku, the Hospital Vice Director in charge of crisis management and disaster prevention, was assigned the post as the third General Manager. In April 2017, Professor Dr. Naoto Morimura was assigned the post as the fourth General Manager of the Department of Disaster Medical Management and was appointed as the chairman of the in-hospital Disaster Prevention Committee.

This department belongs to the Central Clinical Facilities Division and is involved in activities within this hospital and inside/outside of the University.

In order to establish disaster medical management studies, we are aiming at 1) fostering leaders who can develop plans for disaster medicine and educate personnel engaged in disaster medicine, 2) relationship building with relevant institutions for establishing a system for the University of Tokyo Hospital to lead disaster medicine and 3) developing a system as a base of formation of organizations at the time of disaster.

## Clinical activities

Since 2012, the Disaster Prevention Committee carries out planning and conduct the University of Tokyo Hospital Comprehensive Disaster Drill regularly. Drills of launching a new earthquake early warning system, building hospital headquarter for disaster control, reporting in-hospital damage situation, establishing triage and casualty clearing station, triage and rescue of mass casualties, were performed yearly with cooperation of the University of Tokyo, the Metropolitan Tokyo Fire Department, and the Ministry of Health Labor and Welfare.

## Teaching activities

As educational activities inside and outside of the University, we are holding and teaching MIMMS, Major Incident Medical Management and Support, courses accredited by English ALSG, Advanced Life Support Group, regularly for the purpose of developing leadership of health care professionals who can provide ideal medical care in times of disaster. Also, we are cooperating holding and

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

## Research activities

We are seeking ways of cooperation between institutions through workshops with relevant institutions from the perspective that day-to-day cooperation with relevant institutions can be also utilized at the time of disaster. We consider that it can be also utilized for cross-business formation of organizations at the time of disaster.

Other than that, we are holding outside research groups and cooperating for building up a functional emergency medical system at the time of disaster.

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# International Medical Center

**Director and Associate Professor**

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## Introduction and Organization

One of the University of Tokyo's significant challenges is globalization. The International Medical Center was launched as a significant step forward in enhancing The University of Tokyo Hospital's development as an international hub. Designated director 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. In the past, some foreign patients have successfully received treatment thanks to the support of individual departments. However, from henceforth, 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 sophisticated 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 advanced clinical trainees granted permission 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. Internal hospital rules to accept consultant level foreign medical doctors as Invited Faculty member has also been settled.

Lastly, heightening the capability of physicians and medical staff to cater to international needs is an important factor in globalizing The University of Tokyo Hospital. To this end, the International Medical Center will attempt to cultivate personnel by hosting various international exchanges and language-training programs so as to further develop the hospital's capabilities to become an international hub in the field.

# Department of Clinical Nutrition Therapy

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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, the standard food service approval system was abolished, and 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 that the Tokyo Diabetes Association held to the side of the free space in the vestibule of the outpatient department. In the first year there were 3527 visitors a week.

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 to the staff (full time) as a full-time employee to calculate the billing charges for the NST was approved. 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. The renovation of the main kitchen was determined for the purpose of introduction of the New Cook Chill System.

## 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.

The records of achievements in 2015 show that there were 2819 instances of inpatient nutritional guidance (455 without charge) and 5503 instances of outpatient nutritional guidance (275 without charge). The results for group nutritional guidance showed that during the year there had been 292 outpatient diabetes classes and 217 inpatient diabetes classes (for some of which there was a charge), and that there had been 115 best-weight classes, classes after gastric cancer operations for 81 patients, and mother's classes for 139 mothers.

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

131 guidance sessions in 2015.

In April 2014, the department started calculating charges for NST and counted 1261 instances in the first fiscal year, which reached 1529 instances in 2015.

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 the fiscal year of 2016, 8858 instances were monitored in this system.

In April 2015, alternative initial screening criteria specific for pediatric and pregnant patients were added to the procedure manual of nutritional management, respectively.

- **Educational Activities**

The Department accepts managerial dietitian clinical trainees. In 2015, the department accepted 41 trainees from 7 training schools: Ochanomizu University, Tokyo Kasei University, Otsuma Women's University, Kagawa Education Institute of Nutrition, Jissen Women's Educational Institute, Japan Women's University, and Wayo Women's University.

In 2011, the Department began accepting NST trainees. From 1 to 4 or 5 terms are conducted a year (5 days/ week/ term). Participants are mainly managerial dietitians, pharmacists, nurses, medical technologists, and physical therapists, and candidates are trainees whose aim is acquiring the qualifications certified by academic societies or to become a full-time employee to calculate the billing charges for the NST. There were 17 participants (7 managerial dietitians, 5 pharmacists, 5 nurses) in 2015.

To disseminate NST activities fully in the hospital, the department organizes NST Seminar for Doctor-in-training and Clinical Nutrition Seminar throughout the year. 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. The ratio of completion reached 99.0% in March 2016. In December 2016, the exchange training program between the Department of Nutrition Management of The Institute of Medical Science and our department was initiated. At the same month, "The Manual of The Department of Clinical Nutrition Therapy 2015-2016" was published.

## Research

- Joint research with the Department of Stomach and Esophageal Surgery
  Research topics: "Evaluation of nutrition indexes after proximal gastrectomy"
  "Multi-center randomized controlled study of the effects of early post-gastrectomy oral feeding support"
  "A randomized study of post-operative invasiveness and systematic post-operative functional assessment in esophageal cancer comparing the operation procedures"

- Joint research with the Department of Hepatobiliary and Pancreatic Surgery
  Research topic: "Assessment of perioperative improvement in nutrition status by an open trial of an immune-enhancing diet in patients who have undergone pancreaticoduodenectomy"

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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.

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

Joint Meeting

In 2016, several medical laboratories from Shimane University and our laboratory jointly held a Scientific Meeting in Oki Island. The members from the both universities including the teaching staffs, graduate students and researchers, as well as some high school students in Oki Island, fully enjoyed this retreat, 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 two 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), and the CREST joint meetings in 2014 and 2015 (hosted by Kumamoto University and the University of Tokyo). We will keep planning such Joint Meetings in the future.

Seminar hosted by our lab (co-sponsorship: MPUTC, Laboratory of Animal Resouces)

Title: RNA modified bases & grammar education for the naïve immune system / Dr. Vincent P. Kelly (Trinity College Dublin, Ireland)

In July 2016, we organized an invited lecture by Dr. Vincent P. Kelly introducing his continuing efforts to understand the function and activity of a highly unusual RNA base referred to as queuine.

List of labs:

Prof. Wan-Wan Lin's Laboratory, National Taiwan University

Prof. Shie-Liang Hsieh's Laboratory, National Yang-ming University

Prof. Ken-ichi Yamamura's Laboratory, The University of Kumamoto

Prof. Toru Nabika's Laboratory, Shimane University

Prof. Seiji Yamaguchi, Shimane University

Prof. Toru Miyazaki's Laboratory, The University of Tokyo

DBELS (Disease Biology Excellent Lecture Series)

We present a lecture series by top scientists in a variety of research fields related to disease biology. So far, eleven lecturers have been invited from many places including Kyoto Univ., Hokkaido Univ., Riken Institute, Tokyo Univ. of Science, Washington Univ. (USA), Univ. of Basel (Switzerland), and Weill Medical College of Cornell University (USA).

DBELS-EXTRA

This is a lecture series on the latest experimental techniques for medical research, founded as an extension of DBELS. We offer monthly lecture series, each of which convenes twice to four times a month, aiming mostly at graduate students and junior researchers.

This series provides lectures by experts from companies, universities and research institutions specializing in a wide range of areas such as molecular biology, cellular biology, genetics, immunology and others.

DBELS WORKSHOP

In 2007, we had a workshop at Unzen, a great resort place in Nagasaki prefecture. Along the policy for DBELS, we invited 8 top scientists from Kyoto, Tokyo, Hokkaido, Okinawa, and Boston as lecturers, and many young participants as audiences. Staying in a beautiful resort hotel, we all had a scientifically and culturally fruitful time. The next workshop is scheduled to be held in Switzerland, probably in 2010 summer.

Music and Science

On Jun 6, 2006, to commemorate the foundation of

our lab, we organized an invited recital by Mr Maestro Krystian Zimerman, a world-famous pianist, followed by a debate session on music and science between Mr. Zimerman and Professor Miyazaki at Yasuda Auditorium with more than 800 audiences.

Visiting Professors

We welcomed Prof. Wakeland from Southwestern Medical Center at The University of Texas in fiscal 2006, and Prof. D. Mathis and Prof. C. Benoist (immunology) from Harvard University in fiscal 2007, all of whom belonged to our lab as a guest professor for three months respectively.

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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.

## Teaching activities

We have 1 master course and 4 doctor course students in 2016. We were also responsible for undergraduate education of physiology, and organized all lectures, student experiments and examinations. We gave all together 8 lectures of physiology for undergraduate students, and 5 lectures of physiology and neuroscience for master course students. Four undergraduate students join 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. We will explain one representative work (Ref. 4) of this year in some detail.

The majority of excitatory synaptic contacts are formed by small dendritic protrusions in the cerebral cortex, commonly referred to as dendritic spines. The growth and shrinkage of dendritic spines are typically determined by cytosolic $Ca^{2+}$ levels, and they, respectively, underlie the long-term potentiation and depression of synaptic connectivity._In addition, the generation and elimination of spines are reported to be induced by tasks involving learning and memory, albeit at a slower rate than processes governing enlargement and shrinkage[4-6]. Spine turnover has been traditionally observed following activity-dependent plasticity induced by cytosolic increases in $Ca^{2+}$ concentration, but has also been identified in the absence of specific learning tasks. Such intrinsic dynamics are reported to occur *in vitro* in a $Ca^{2+}$-independent manner. However, to the best of the authors' knowledge, no study has directly investigated whether the baseline rate of spine turnover reflects non-specific learning under normal rearing conditions, or activity-independent intrinsic dynamics *in vivo*.

Notably, the baseline rate of spine turnover is reported to be augmented in several *in vivo* models of autistic spectrum disorder (ASD). Fragile X syndrome, the most prevalent monogenic form of ASD, is caused by the expansion of CGG repeats upstream of the coding region in the *FMR1* gene, leading to reduction of the fragile X mental retardation protein (FMRP). *Fmr1* knockout (KO) mice present with many of the neural abnormalities observed in patients with fragile X syndrome, including abnormalities in dendritic spine morphology, synaptic plasticity, and learning and memory. Moreover, spine turnover is similarly increased in *Fmr1* KO mice, as observed in other models of ASD. However, no studies have examined whether the increased rate of baseline turnover observed in ASD models reflects activity-dependent plasticity or activity-independent intrinsic dynamics, and therefore the mechanism responsible for increased spine turnover in ASD models remains largely elusive.

With regard to previous *in vivo* neuroimaging techniques, studying the activity-dependent nature of basal spine turnover in the neocortex was difficult using methods such as cranial glass windows or thinned skulls. Because animals are unable to survive when cortical activity is abolished, neuronal $Ca^{2+}$ signaling must be locally silenced in small regions, wherein the time-lapse imaging of dendritic spines can be performed. To resolve this issue, inhibitors of $Ca^{2+}$ signaling were infused locally into the visual cortex via a microfluidic brain interface, and two-photon time-lapse imaging was performed in this region. $Ca^{2+}$ signaling and learning-induced spine turnover were evaluated in wild-type and *Fmr1* KO mice after treatment with $Ca^{2+}$ signal inhibitors. Reports indicate that matrix metalloproteinase 9 (MMP9) KO rescues various abnormalities observed in *Fmr1* KO mice, including structural spine abnormalities. As MMP9 inhibitors have also been linked to changes in spine structure.

In wild-type and *Fmr1* KO mice, the majority of baseline turnover was found to be activity-independent. Accordingly, the application of matrix metalloproteinase-9 inhibitors selectively restored the abnormal spine dynamics observed in *Fmr1* KO mice, without affecting the intrinsic dynamics of spine turnover in wild-type mice. Such findings indicate that the baseline turnover of dendritic spines is mediated by activity-independent intrinsic dynamics. Furthermore, these results suggest that the targeting of abnormal intrinsic dynamics might pose a novel therapy for ASD (Ref.4).

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# Laboratory of Biomedical Equipment and Biomaterials

**Professor**

Takashi Azuma, Ph.D.

**Associate Professor**

Taichi Ito, Ph.D.

**Assistant Professor**

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## Introduction and Organization

The Division is composed of two laboratories, Azuma laboratory and Ito Laboratory. The Division tightly collaborates with Faculty of Engineering. Prof. Azuma is also charged at Department of Mechanical Engineering and Bioengineering, where the laboratory members include an assistant professor, two associates and 3 graduate students. Prof. Ito charged at Department of Chemical System Engineering and Bioengineering. The current laboratory members include one assistant professor, two associates, and 13 graduate students School of Engineering and Medicine.

## Teaching activities

Prof. Azuma and Prof. Ito are sharing duties for undergraduate and graduate students of both Graduate School of Medicine and Graduate School of Engineering. They give lectures on biomedical engineering at Graduate School of Medicine. Prof. Azuma has also lectures on Overview of Bioimaging, Overview of Mechano-Bioengineering, Bioengineering exercise for social implementation at Graduate School of Engineering. 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

Prof. Azuma's laboratory aims to develop clinical imaging and therapeutic systems. In particular, we 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.

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

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# Laboratory of Clinical Biotechnology

**Professor**

Yuichi Tei/ Ung-il Chung, M.D.,Ph.D. (November, 2016－)

**Associate Professor**

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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 the Vice Program Coordinator of the Graduate Program for Leaders in Life Innovation (GPLLI) and as Research Leader of The University of Tokyo Center for Innovation (COI) Self-Managing Healthy Society. In collaboration with these programs, 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). 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. 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 Communications* 376:375, 2008; *Journal of Bone and Mineral Metabolism* 28:627, 2010).

4. The development of tissue-inductive implant devices integrating tissue-regeneration signals and highly functional and biocompatible biomaterials

In the current aging society, the treatment of tissue defects in locomotive organs is a crucial task to achieve the extension of healthy life expectancy. There is an urgent need for low-invasive reconstruction therapies that recover lost or damaged tissues with the same functional and aesthetic qualities as those in healthy states. The transplantation of donor tissues obtained from patients' healthy sites has been widely used for tissue reconstruction (autologous transplantation). However, this strategy often causes post-operative pain and the cosmetic disturbance of donor sites. Although reconstruction with biomaterials avoids donor site problems, its tissue induction capacity is generally inferior to that of autologous transplantation.

As signaling networks mediating the formation and regeneration of tissue and organs are being elucidated by recent advances in stem cell biology, some biomaterial-based systems are being developed for delivering signaling factors to target tissues. We are studying these approaches as mentioned above. In addition, the emergence of three-dimensional (3D) printers has rapidly improved the techniques available for controlling the shapes of scaffold materials. By controlling the 3D shape of biomaterials, we have been attempting to improve the performance of biomaterials for tissue repair. We developed custom-made calcium phosphate artificial bone (CT-bone) that is manufactured using 3D printers and have applied them to clinical settings in cooperation with the Department of Oral and Maxillofacial Surgery, The University of Tokyo Hospital (*Journal of Artificial Organs* 9:234, 2006; *Journal of Artificial Organs* 12:200, 2009; *Regenerative Therapy* 5:1, 2016). We have also worked on the development and application of tetrapod-shaped calcium phosphate artificial bone (Tetrabone), which is fabricated at 1-mm size by injection molding, and a custom-made titanium mesh cage fabricated by laser sintering (*Acta Biomaterialia* 8:2340, 2012; *Biomaterials* 35:3229, 2014).

However, either signaling factors or biomaterials alone are not sufficient for the clinically sufficient regeneration of tissues, and interface units integrating them are necessary for fully utilizing their performance. A candidate for the integrating interface unit is a high-performance hydrogel unit, which maintains the spatial arrangement of signaling factors and can deliver them to target cells at a selected timing by temporally controlled degradation. However, conventional hydrogels do not provide the characteristics required for an integrating interface unit.

In cooperation with 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). The high-performance hydrogel unit would integrate signaling factors with shape-controlled scaffold materials, leading to the development of implant devices that work as scaffolds for tissue repair and also as carriers of bioactive factors. Through a series of these studies, we are aiming to create a "four-dimensional scaffold system" that achieves efficient tissue regeneration by controlling cell proliferation and differentiation in temporal and spatial manners. The system will not only be applicable to the regeneration of other tissues; it will also contribute to the development of basic technologies for the temporal-spatial control of *in situ* tissue formation, which is versatile in the prevention, diagnosis, and treatment of various diseases.

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administration of a hedgehog agonist accelerates fracture healing in a mouse model. Biochem Biophys Res Commun 2016;479(4):772-8.
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# Laboratory of Environmental Health Sciences

**Associate Professor**

Seiichiroh Ohsako, Ph.D., D.V.M.

## Introduction

Laboratory of Environmental Health Sciences of the Center for Disease Biology and Integrative Medicine moved the laboratory moved from the 3rd floor of the Medical Faculty of Medicine Building 1 to Clinical Research Center-A on October 2016. One associate professor, one temporal researcher, one visiting researcher, two doctoral students, two master course student students, and a graduation trainee conducted researches together during the year of 2016.

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.

## Research activities

Laboratory of Environmental Health Sciences was constituted by members who were formerly working in the National Institute for Environmental Studies. The laboratory focused on influence the low-level exposure of the environmentally pollutant chemicals to the fetal and neonatal periods which is the vulnerable developmental stage. To study the pathology and developmental abnormalities after adulthoods, toxicity studies by orthodox animal experiments were employed to clarify the involvement of related molecules in pathogenesis.

DOHaD (Developmental Origin of Health and Diseas) is a generalized academic concept in recent years, and chemical exposure is regarded as an important environmental factor in DOHaD. Until now, in our laboratory, we were investigating what kind of adverse effect will be left to offspring that have been born by administering dioxin (TCDD) and bisphenol A (BPA). These compounds are exposed to human in an inevitable unintended way from the environment. Although the dioxin problem seems to have calmed down by strengthening the installation standard of the incinerator which is a major source of dioxin, however, there are still many unknown parts regarding the molecular mechanism of its various toxicity manifestations, especially the endocrine disrupting mechanism. In addition, BPA is experimentally shown the influence on reproductive function and brain development in plastics materials used all over the world. Regulations in Canada and Europe are becoming more stringent in recent years.

The above-mentioned substances are only an example, and tens of thousands of new chemical substances unknown toxic influence in the world are diffused globally when they appear constantly. It is an inevitable process for modern civilization to regulate each time with scientific grounds. The mission of this laboratory is to identify the substances of concern before actual damage of ecological impact / health effects occurs, and further to determine what kind of biological effects are present from animal experiments.

Epigenetic Toxicology: DOHaD has been payed attentions because the effects of unbalanced nutrition and chemical exposures may remain as epigenetic changes imprinted by the fetal environment, not but as non-genetic phenotype. In our laboratory, I found that DNA methylation level of the promoter region of drug metabolizing enzyme gene (Cyp1a1) in the mouse liver is down-regulated by TCDD exposure and this hypomethylation is dependent on Ahr gene. I also found that this hypomethylation is irreversibly caused by fetal exposure. Since the dissociation tendency of

Dnmt3b was observed at the beginning of birth, I hypothesized that it may be passive demethylation. However, even when administered to mature individuals of high-dose TCDD, the hypomethylation occurred in a very short time without cell division, and thus it was considered to be an active demethylation mechanism. Therefore, we found that molecules that control base excision repair (Tet1, Tet2, Tet3, Tdg, Apex1) are also activated by Ahr-TCDD and for the first time, nuclear receptor-dependent demethylation mechanism (Amenya et al., 2016).

MSD-AFLP method: In order to analyze the exhaustive methylation profile of genome-wide at high accuracy, next-generation sequencers are currently used. In these methods, high depth is required, therefore there is a problem of cost efficiency. In environmental toxicology and molecular epidemiology of humans, it is necessary to reduce expenses in order to analyze multiple samples. MSD-AFLP method was developed by our laboratory as a low-cost genome-wide CpG methylation analysis. A unique library preparation protocol, MSD, for amplifying only a DNA restriction enzyme fragment having methylated CpG at the ends was combined with an AFLP method. This technique is able to detect differences in methylation of 5% between samples with specific CpG (Aiba et al., 2017).

## Teaching activities

The Laboratory of Environmental Health Sciences has important missions to train postdoctoral fellows to become promising scientist leaders in the field of environmental toxicology and to give toxicology and environmental health courses for graduate and undergraduate students. The following lectures have been provided to students.

Graduate education

Lectures, Seminar, and laboratory practice, as well as guidance for the dissertation for the Master's and Doctor's degrees have been provided.

Master Course in the Graduate School of Medical Sciences: Toxicology (Lecture)

Master and Doctor Courses in the Graduate School of International Health: International Environmental Medicine (Lecture and Laboratory Practice)

Master Course in the School of Public Health: Environmental Health Medicine (Lecture)

## Publications

**Original article:**

1. Aiba T, Saito T, Hayashi A, Sato S, Yunokawa H, Maruyama T, Fujibuchi W, Kurita H, Tohyama C, Ohsako S. Methylated site display (MSD)-AFLP, a sensitive and affordable method for analysis of CpG methylation profiles. BMC Mol Biol 18(1):7, (2017)
2. Amenya HZ, Tohyama C, Ohsako S. Dioxin induces Ahr-dependent robust DNA demethylation of the Cyp1a1 promoter via Tdg in the mouse liver. Scientific Reports 6:34989, (2016)
3. Yamane J, Aburatani S, Imanishi S, Akanuma H, Nagano R, Kato T, Sone H, Ohsako S, Fujibuchi W. Prediction of developmental chemical toxicity based on gene networks of human embryonic stem cells. Nucleic Acids Res. 44(12):5515-28. (2016)

# Laboratory of Animal Resources

**Professor**

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**Associate Professor**

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**Assistant Professor**

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## Introduction and Organization

Our laboratory was established as the Division of Animal Research affiliated with the Faculty of Medicine in April 1971. The building for animal experimentation was completed and the accommodation and experimentation of laboratory animals started in 1973. In 2003, the laboratory was reorganized as the Section of Animal Research of the Center for Disease Biology and Integrative Medicine (CDBIM). In 2008, the Laboratory of Animal Resources was established to strengthen research activities in addition to the Section of Animal Resources. The members of our laboratory and section are 6 teaching staffs, 3 technical support staffs, an assistant manager of CDBIM, an administrative staff, a project academic support specialist, 4 assistant laboratory animal technicians, and 3 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 917 at the end of academic year 2016.

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 learning and memory. We also study cell metabolism. We generate knockout mice and transgenic mice of signal transduction molecules including the glutamate receptors and mammalian target of rapamycin (mTOR). We applied proteomics analysis to these mice. We also try to generate murine models for human genetic diseases. We have also established new gene targeting technology using the CRISPR/CRISPR-associated (Cas) system.

**1. Cryopreservation of marmoset embryos**

Common marmoset (*Callithrix jacchus*) is a non human primate and recently used for human model, especially focusing on brain function. We have established the techniques for in vitro fertilization. We have cryopreserved 8-cell embryos by vitrification technique, and stored in liquid nitrogen. Frozen embryos were thawed and subjected to blastomere ablation experiments. After ablation, we succeeded in extracting genomic DNA from blastomeres for genotyping.

**2. Generation of knock-in mice by CRISPR/Cas system**

The CRISPR/Cas system has rapidly emerged recently as a new tool for genome engineering, and is expected to allow for controlled manipulation of specific genomic elements in a variety of species. A number of recent studies have reported the use of CRISPR/Cas for gene disruption (knockout) or targeted insertion of foreign DNA elements (knock-in). Despite the ease of simple gene knockout, small insertions or nucleotide substitutions in mouse embryos, targeted insertion of large DNA elements remains an apparent challenge. We tried to quantify knock-in efficiency using sgRNAs or crRNA/tracrRNA targeting for mouse *Grm1* locus, single stranded oligo DNAs as donors and Cas9. We have succeeded to maximize knock-in efficiency (63.0%), when purified Cas9 protein was injected with crRNA/tracrRNA and donor DNA.

**3. Generation of calsyntenin triple KO mice**

Calsyntenins are membrane proteins belonging to cadherin superfamily. In *C. elegans*, a calsyntenin homolog CASY-1 is required for taste avoidance learning. There are three mouse calsyntenins (CLSTN1, 2, and 3), which are predominantly expressed in the central nervous system (CNS). To investigate the role of CLSTNs in the CNS, we plan to generate *Clstn* triple KO mice. We have injected Cas9 mRNA with sgRNA targeting *Clstn* 1, 2 and 3 into mouse embryos and have obtained founder mice which carry several mutant alleles of *Clstn* genes. By crossing these mice, we have established *Clstn* triple KO mice. *Clstn* triple KO mice are viable. We examined long-term potentiation (LTP) in the TKO hippocampus and found that they induce normal LTP. We are currently examining the behavior and analyzing the brain structure by immunehistochemistry.

**4. 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 7% of patients have a smaller, nested deletion of 1.5 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. These mice showed abnormalities in heart and thymus that are often observed in 22q11.2DS patients.

## References


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# Laboratory of Molecular Radiology

**Professor**

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

**Lecturer**

Noriko Hosoya, M.D., Ph.D., Atsushi Enomoto, Ph.D.

**Associate**

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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 radio-active materials frequently take place.

## Research

We focus on the mechanism underlying the cellular response to DNA double-strand breaks (DSBs). Among various types of DNA damage, DSBs are the most deleterious if not repaired properly. To protect the genome, at least four signaling cascades are known to function as the repair machineries against

DSBs. While nonhomologous end joining, microhomology-mediated end joining, and single-strand annealing are error-prone repair pathways, homologous recombination (HR) is an error-free pathway in principle using newly replicated DNA as a template for the repair. There is accumulating evidence that defective HR plays a role in tumor development. For example, BRCA1 and BRCA2, tumor suppressors in hereditary breast and ovarian cancers, are known to mediate the damage response to DSBs and promote HR.

Rad51, a key player at early stages of HR, catalyzes the invasion of a single-strand DNA end into an intact homologous duplex. BRCA2 plays a mediator role at this stage by directly binding to Rad51 and promoting the formation of the filament consisting of the single-strand DNA and Rad51.

SYCP3 is a component in the synaptonemal complex which is formed between homologous chromosomes to ensure their connection in meiosis. Expression of SYCP3 was observed in adrenal, liver, stomach, and kidney tumors, confirming that SYCP3 is a cancer testis antigen. Treatment of SYCP3-nonexpressing cells with a methylation inhibitor induced its expression, indicating that methylation alteration in cancer is responsible for its ectopic expression.

Since biological significance of cancer testis antigens in somatic cells is largely unknown, we investigated the effects of SYCP3 expression on cellular functions in somatic cells. This study revealed that SCYP3-expressing cells are hypersensitive to radiation or 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.

In addition to Rad51, Rad51 paralogs, Rad54, and Rad54B are also involved in HR. While Rad51 paralogs and Rad54 were shown to assist the Rad51-dependent cascade, the involvement of Rad54B in HR is not closely associated with Rad51and Rad54. This fact led us to hypothesize that Rad54B has a role distinct from other HR factors. We found that levels of Rad54B are inversely correlated with protein levels of p53 both after DNA damage and Rad54B knockout cells. Protein interaction analysis revealed that Rad54B promotes proteasome-dependent degradation of p53 by directly binding to MDM2/MDMX, an E3 ubiquitin ligase complex targeting p53. Furthermore, we found that over-expression of Rad54B facilitates genomic instability by negatively regulating cell-cycle checkpoints medicated by p53. Consistent with this biological function, high levels of Rad54B were shown to correlate with poor prognosis in colorectal cancers.

Thus, our studies on the mechanisms underlying HR contribute to the establishment of important strategies against cancer. Radiation and many DNA-damaging chemotherapeutic agents induce DNA DSBs, which can be normally repaired by the intrinsic repair pathways. The induced breaks therefore do not always lead to apoptosis. If we will understand the details of the repair pathways, the molecules in this pathway will be the therapeutic targets. From the clinical point of view, we are continuing the research exploring the principle in this field.

## Publications

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# Office of International Academic Affairs

**Head**

Yasuyuki Seto

**Assistant Professors**

Joseph Green

Christopher Holmes

Keiko Nanishi

**Homepage http://koryu.m.u-tokyo.ac.jp**

## Status and functions

The Office of International Academic Affairs 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 i) international educational exchange, ii) international contacts in research and scientific fields, and iii) international cooperation in health care and medicine.

## Activities

This document reports on the office's activities in these areas over the 2016 academic year (April 1, 2016 through March 31, 2017).

### 1. International Educational Exchange

1.1 Student counseling about education and research

In 2016, there were 133 foreign students (38 countries) officially registered in the Graduate School of Medicine. Many inquiries were received during this period from prospective applicants for foreign student and trainee status; responses were sent to 51 such inquiries.

Many currently enrolled foreign students received counseling at this office concerning their studies and life at the University of Tokyo and the requirements for obtaining scholarships and degrees.

In addition, a large number of University of Tokyo students wish to supplement their training with basic clinical experience overseas before graduation, as well as the type of short-term training (1-3 months) frequently called clinical electives overseas. Inquiries from these students were either answered by this office or referred to appropriate centers.

Every year, 25 or more University of Tokyo students go overseas to study, and the office makes its best efforts to accommodate their needs.

It has become a tradition to hold a Spring get-together of foreign students and University of Tokyo students who will study or have studied abroad. This event is attended by the Dean of the Faculty of Medicine, teaching staff, administrative staff, and students; about 70 people attended in 2016, at the Sanjo Kaikan, a reception hall on the Hongo campus.

A formal agreement for academic exchange between the University of Pennsylvania and the University of Tokyo was renewed in May 2004. Since that time, sixteen University of Tokyo students have taken research electives at the University of Pennsylvania, and two students from the University of Pennsylvania have taken clinical electives at the University of Tokyo.

An agreement on academic cooperation was signed between the Graduate School of Medicine of the

University of Tokyo and Johns Hopkins University in December 2002. Since the start of the program in 2002, twenty-nine University of Tokyo students have visited to attend clinical electives at Johns Hopkins University, and four students from Johns Hopkins University have taken clinical electives at the University of Tokyo.

An agreement on academic cooperation was signed between the Graduate School of Medicine of the University of Tokyo and the University of Michigan Medical School in January 2005. Since the start of the program in 2005, twenty-one University of Tokyo students have attended clinical electives at the University of Michigan Medical School, and eleven students from the University of Michigan have taken clinical electives at the University of Tokyo.

An agreement on academic cooperation was signed between the Graduate School of Medicine of the University of Tokyo and Munich University in February 2005. Since the start of the program in 2005, fourteen University of Tokyo students have visited to attend research electives at Munich University, and ten students from Munich University have taken clinical electives at the University of Tokyo.

An agreement on academic cooperation was signed between the Graduate School of Medicine of the University of Tokyo and the College of Medicine of Taipei Medical University in November 2005. Since the start of the program in 2005, five University of Tokyo students have visited to attend clinical electives at Taipei Medical University and fifteen students from Taipei Medical University have taken clinical electives at the University of Tokyo.

An agreement on academic cooperation was signed between the Graduate School of Medicine of the University of Tokyo and the College of Medicine of National Taiwan University in October 2012. Since the start of the program in 2012, six University of Tokyo students have visited to attend clinical electives at National Taiwan University and eight students from National Taiwan University have taken clinical electives at the University of Tokyo.

An agreement on academic cooperation was signed between the Graduate School of Medicine of the University of Tokyo and the University of Chicago Medicine in June 2014. Since the start of the program in 2014, three University of Tokyo students have visited to attend clinical electives at the University of Chicago Medicine.

An agreement on academic cooperation was signed between the Graduate School of Medicine of the University of Tokyo and Sydney Medical School in June 2015. Since the start of the program in 2015, three University of Tokyo students have visited to attend clinical electives at Sydney Medical School and three students from Sydney Medical School have taken clinical electives at the University of Tokyo.

1.2 Counseling about short-term and longer overseas study programs for University of Tokyo medical students and researchers.

Every year, about 35 requests from students for counseling regarding pre-graduation or post-graduation studies abroad are received by the Office of International Academic Affairs. The office responds to these requests by providing information, advice, and letters of recommendation.

## 2. Education and research

2.1 Education

In 2016, Dr. Green taught courses open to all students in the Graduate School of Medicine: Introduction to Scale Development 1 and 2. Dr. Green also taught two other graduate-level classes: International Epidemiology 1 and 2.

Mr. Christopher Holmes taught Medical English 1 and 2, which are required for all medical students.

The Office also organized classes in English for the Health Sciences. In 2016, Mr. Holmes also arranged and led ad hoc sessions in Oral Presentation Training and extracurricular activities in English for medical students and graduate students. These sessions were open to all students and teaching staff in the Graduate School of Medicine and the Faculty of Medicine.

Dr. Green and Dr. Nanishi conducted several international health studies.

2.2 Publications

1: Pokhrel K, Nanishi K, Poudel KC, Pokhrel KG, Tiwari K, Jimba M. Undernutrition Among Infants and Children in Nepal: Maternal Health Services and Their Roles to Prevent it. Matern Child Health J. 2016 Oct;20(10):2037-49.

2: Maulida R, Nanishi K, Green J, Shibanuma A, Jimba M. Food-choice motives of adolescents in Jakarta, Indonesia: the roles of gender and family income. Public Health Nutr. 2016 Oct;19(15): 2760-8.
3: Enuameh YA, Okawa S, Asante KP, Kikuchi K, Mahama E, Ansah E, Tawiah C, Adjei K, Shibanuma A, Nanishi K, Yeji F, Agyekum EO, Yasuoka J, Gyapong M, Oduro AR, Quansah Asare G, Hodgson A, Jimba M, Owusu-Agyei S; Ghana EMBRACE Implementation Research Project Team. Factors Influencing Health Facility Delivery in Predominantly Rural Communities across the Three Ecological Zones in Ghana: A Cross-Sectional Study. PLoS One. 2016 Mar 31; 11(3):e0152235.
4: Holmes C. Have you ever read a medical novel? J Med Eng Educ. 2016; 15(3): 133-137.

# MD Scientist Training Program

**Professor and Director**

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

**Assistant Professor**

Yuki Sugaya, M.D., Ph.D.

Ikuko Honda, Ph.D.

**Homepage: http://www.ut-mdres.umin.jp/ (in Japanese)**

## Introduction and Organization

The MD Scientist Training Program (MDSTP) was founded in 2008 to achieve the goal of systematically providing an intensive basic medical research training framework to the next generation of MD scientists during their MD training at the School of Medicine, The University of Tokyo. Capitalizing on the advances made by launching a reliable and sustainable program through the leadership of its first directors, Prof. Shigeo Okabe (2008-2010) and Prof. Masahide Kikkawa (2011-2014), the Program currently consists of its director Prof. Haruhiko Bito and two assistant professors Yuki Sugaya and Ikuko Honda, and over 80 students who are seeking extracurricular basic medical research training through the Program's framework. With the help of two assistants for clerical work, it provide 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 80 students (during Year 3 to 6 of the Medical School). Around 10 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 2016, a total of 4 students received the Program's support for carrying out basic medical research abroad (in US, Europe and Australasia) for more than a month and to present their research achievements at international scientific meetings. We also support exposure to clinical training in foreign hospitals with the Osamu Otsubo Tetsumon Fellowship, initiated in 2008 with an Endowment donated by Dr. Osamu Otsubo. In 2016, a total of 16 students were awarded a fellowship and gained invaluable experience as student clinical clerks in many university hospitals abroad.

2) Organizing an MD scientist training program retreat

A MDSTP retreat was held on March, 19-20, 2017 to present ongoing research progress in a closed meeting among peers. More than 40 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, Annual Joint Retreats were held to promote communication and networking among the medical students with research minds. The latest retreat was organized on March, 21-22, 2015 in Kobe, at the occasion of the joint annual meeting of The Japanese Association of Anatomists and Physiological Society of Japan. More than 100 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. Eight selected students presented their research achievements in a joint symposium session of this meeting, held in the Main Hall of Kobe International Convention Center.

The MSDTP also currently cooperates with 9 other universities in eastern Japan to organize annual research students' retreats. In 2016, this was held on August, 18-19 in Ikaho, Gunma under the auspices of Gunma University. Around 70 people participated in the retreat and presented their ongoing research progress and future plans.

## Activities (2016)

The number of registered students: 80 (3rd grade: 26, 4th: 23, 5th: 13, 6th: 18)

Lectures for students in Years 1 and 2
Introduction to Medical Biology: 13 lectures
Group reading of Molecular Biology of the Cell: 11 lectures

Seminar for students (in Year 3 or above)
Journal Club for basic medical research: 7 lectures
Medical Research Communications: 28 lectures

Presentation of research progress: 2 times (including the retreat of MD scientist training program in the University of Tokyo)

The number of students receiving travel supports for research and clinical activities abroad: 20

The number of Year 6 students who passed their honors thesis defense: 8 (the Dean's Prize was awarded to 2 students)

Publications:
Sugaya Y, Medical Scientist Training Program of The University of Tokyo, Japanese journal of biological psychiatry, 2016, Sep., 27(3), 147-150

# Museum of Health and Medicine

**Director**

Kazuhiko Ohe

**Associate**

Atsushi Kitade

**Homepage http://mhm.m.u-tokyo.ac.jp/**

## History and overview

The origins of the School of Medicine and the University of Tokyo Hospital can be traced back to the establishment of the Kanda Otamaga-Ike Vaccination Center in 1858. In 2008, it celebrated its 150th anniversary. The Museum of Health and Medicine was planned as part of commemorative projects to celebrate the 150th anniversary of the founding of the School and the Hospital, and was opened on January 20, 2011. One of the themes for the commemorative projects marking the 150th anniversary was the "development of communication between health science and care and society," and the Museum of Health and Medicine forms one of the pillars of this.

In establishing the Museum of Health and Medicine, we renovated the School of Medicine's Central Building (Medical Library), which had originally been instituted as part of the commemorative projects celebrating the 100th anniversary of the founding of the School and the Hospital. The Museum has about 400m$^2$ areas, including about 70m$^2$ of a permanent gallery and 230m$^2$ of special exhibition rooms.

The aims of the Museum are to: (1) provide health and medical information to the public, (2) educate students studying medicine, health care services and related areas, (3) research the history of medicine and health care through archives, instruments and technology, and (4) preserve and investigate valuable medical archives and instruments, etc.

In addition to the permanent gallery exhibiting accomplishments related to the School and the Hospital and its contributions made to modern and contemporary development in Japan, a feature of the exhibitions is that a large space has also been set aside for special exhibitions to promote understanding among the public regarding the latest advances in medical science and health care. Planning and supervision of the permanent exhibition and special exhibition is done with the cooperation of the various research units within the School and the Hospital, other departments within the University, industry, and museums. Special exhibitions will be changed several times a year.

The first permanent exhibition since the opening of the Museum was a display of medical texts and instruments from the early Meiji era, an Ishihara's Color Blind Test Chart and a gastroscope developed at the University. The first special exhibition was related to the beginnings of the School and the Hospital, Entitled "the Challenge to Infectious Diseases". It introduced the history of vaccinations against smallpox, research into infectious diseases conducted in the University and by its graduates since the Meiji era (1868-1912), and the latest knowledge about infectious diseases. The second was "the Secret of Vessel System", which introduced the circulatory system. The third "diagnosis of cancer", the fourth "Our brain", the fifth "Locomotive syndrome", the sixth "Diabetes Mellitus", the seventh "Pediatrics", the eighth "Forensic Medicine", the ninth "the Colon" followed, the tenth "Virus", and the eleventh "Kidney".

Since the opening of the Museum, more than 117,578 people had visited by the end of FY2016.

## Overview of operations

The opening hours are 10:00-17:00. 12:00-13:00 is lunch break. The Museum is closed every Monday and during the New Year holidays (however, it will open if Monday is a public holiday). Admission is free.

# Office for Human Research Studies (OHRS)

**Professor (Director of OHRS)**

Yutaka Yatomi, M.D., Ph.D.

**Professor (Vice Director of OHRS)**

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

**Lecturer**

Yuzaburo Uetake, M.D., Ph.D.

**Homepage: http://www.m.u-tokyo.ac.jp/ethics/ethcom/index.html**
**http://www.u-tokyo-ohrs.jp/**
**Top page of online application system: https://u-tokyo.bvits.com/esct/**

## Introduction and Organization

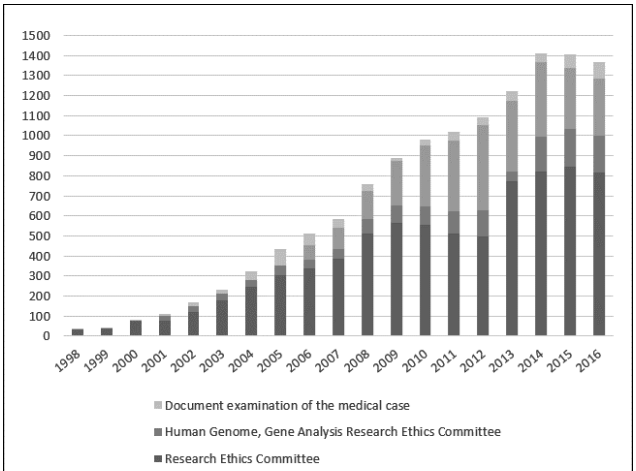
The Office for Human Research Studies (OHRS) was established in October 2009 for the advancement of research ethics standards. OHRS aims to protect the rights, health, and dignity of research participants. Based on this principle, OHRS is providing research ethics support services to researchers at Graduate 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.
- Examination of case documents in connection with,
  -High risk elective operations,
  -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,
- Preperation 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 2016

- Research Ethics Committee (except for clinical trial, GCP):
  383 new applications, 773 minor alterations of approved studies, and 20 documentary examinations
- New clinical documentary examinations: 61




Total number of ethics reviews in Graduate School of Medicine and Faculty of Medicine, The University of Tokyo

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 rise.

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 2016 with 1669 people attended.

OHRS makes efforts to educate researchers through its research ethics support services. Additionally, the skill development and support of the secretariat staff is one of our important tasks.

OHRS also aims to advance research ethics standards by cooperating and consulting with Ethics Consultant specified by each laboratory.

## Research activities

At present, OHRS is a business section. For more information about the research, see the contents of Department of Biomedical ethics, which is a cooperative department.

# The Office for Clinical Practice and Medical Education

**Professor**

Tatsuya Yamasoba, M.D.,Ph.D.

**Assistant Professor**

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

**Homepage none**

## 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 clinical clerkship smoothly, as well as to improve the curriculum and evaluation method by listening to teachers and students. In addition, we try to support an individual student in cooperation with tutors, the instruction department and the office for student assistance in the faculty of medicine. The office now consists of a general manager (professor), an assistant professor, and three clerical assistants.

## Activities

Before clinical clerkship 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 clinical clerkship based on the questionnaire. Just before the start, we hold a ceremony to name students “student doctors”, which the dean 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 clinical clerkship starts, we support teachers and students to run the clerkship smoothly by making necessary contacts with them. Since the opportunities of clinical practice outside the university increased after clinical clerkship began, we have clerical tasks such as mutual contact and paperwork. In addition, we handle problems and considerations occurred during the practice if needed. Particularly, we manage and support students who have difficulties, with the instruction department, a tutor, and the office for student assistance in the faculty of medicine.

Twice a year, we hold a meeting with teachers who are in charge of students’ clinical practice. In this meeting, we provide teachers feedback about comments from students’ questionnaires, and share the information and comments from teachers, and discuss the problems raised by them. Based on the discussion, we make a response or modification to improve clinical clerkship. On the other hand, we have an opportunity to discuss the present condition of clinical clerkship with students, and try to respond to comments from them.

Moreover, we aim at starting the academic affairs system for medical students in UTokyo until the next spring.

# The International Research Center for Medical Education (IRCME)

**Director & Professor**

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**Homepage http://www.ircme.m.u-tokyo.ac.jp/**

## 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 IRCME includes promotion of medical education not only in Faculty of Medicine of the University of Tokyo but also of the whole country, and international cooperation in medical education area in developing countries. 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) Research in international cooperation in medical education area

To find a generalizable methodology for international cooperation in medical education area we contribute to international cooperation for improvement of undergraduate and postgraduate education in the context of status quo of each developing country.

(3) 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 effective ness of such teaching practice and apply it to other medical schools in Japan for future reform.

## Activities of Each Department

**1. Medical Education Studies**

This department promotes research related to medical education field (including health professions education). 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 managers' meeting. Moreover, the department offers direct educational activities such as PBL (problem-based learning) and clinical skill practical training. Medical students are welcomed for free quarter for practical work for research. The department supervises CAT-OSCE (common achievement test-objective structured clinical examination) and gives advices from expert perspectives.

Medical education seminars of the University of Tokyo and basic courses of medical education are monthly held. The department also runs and manages "Tsutsuji no kai" under the consortium with Tokyo Medical Dental University to develop standardized patients indispensable for education of medical interview.

**2. International Cooperation for Medical Education**

This department participates in international cooperation projects and practically works for the research and educational developments in medical education field, undergraduate and postgraduate education in medicine, dentistry, pharmacy, nursing, public health, rehabilitation, etc. in countries mainly in Asia. Furthermore, the department collects information and exchanges human relations for international cooperation in medical education areas domestically and internationally, and supports projects related to medical education.

IRCME invites international experts distinguished in medical education practices or research as visiting faculty members approximately six months per year. Such faculty advises and teaches for planning and implementing the activities of IRCME, and promotes collaborative research.

In 2013, we welcomed a visiting faculty: Dr. Mary Y. Lee (1 Oct 2014 – 27 Mar 2015), Professor of Medicine, Tufts University School of Medicine, Special Advisor for Education Innovation, Tufts Medical Center, Boston, USA

## International Invited Faculty

Dr. Linda Snell