

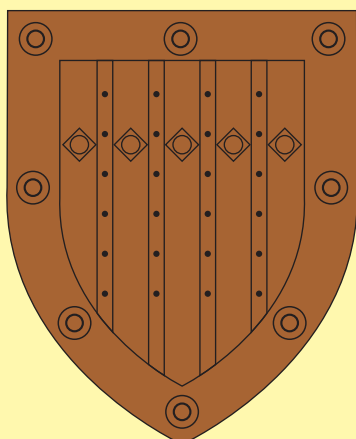
東京医学

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**ANNUAL REPORT OF
THE GRADUATE SCHOOL OF MEDICINE
AND
THE FACULTY OF MEDICINE
THE UNIVERSITY OF TOKYO
REPORTS FOR THE PERIOD April 2010 — March 2011**



共同編集 東京医学会・東京大学医師会・東京大学医学部

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

REPORTS FOR THE PERIOD April 2010-March 2011

Introduction

This is volume 123 (the edition of year 2010) 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.

Takao Shimizu, Dean
Graduate School of Medicine and Faculty of Medicine
The University of Tokyo

March, 2011

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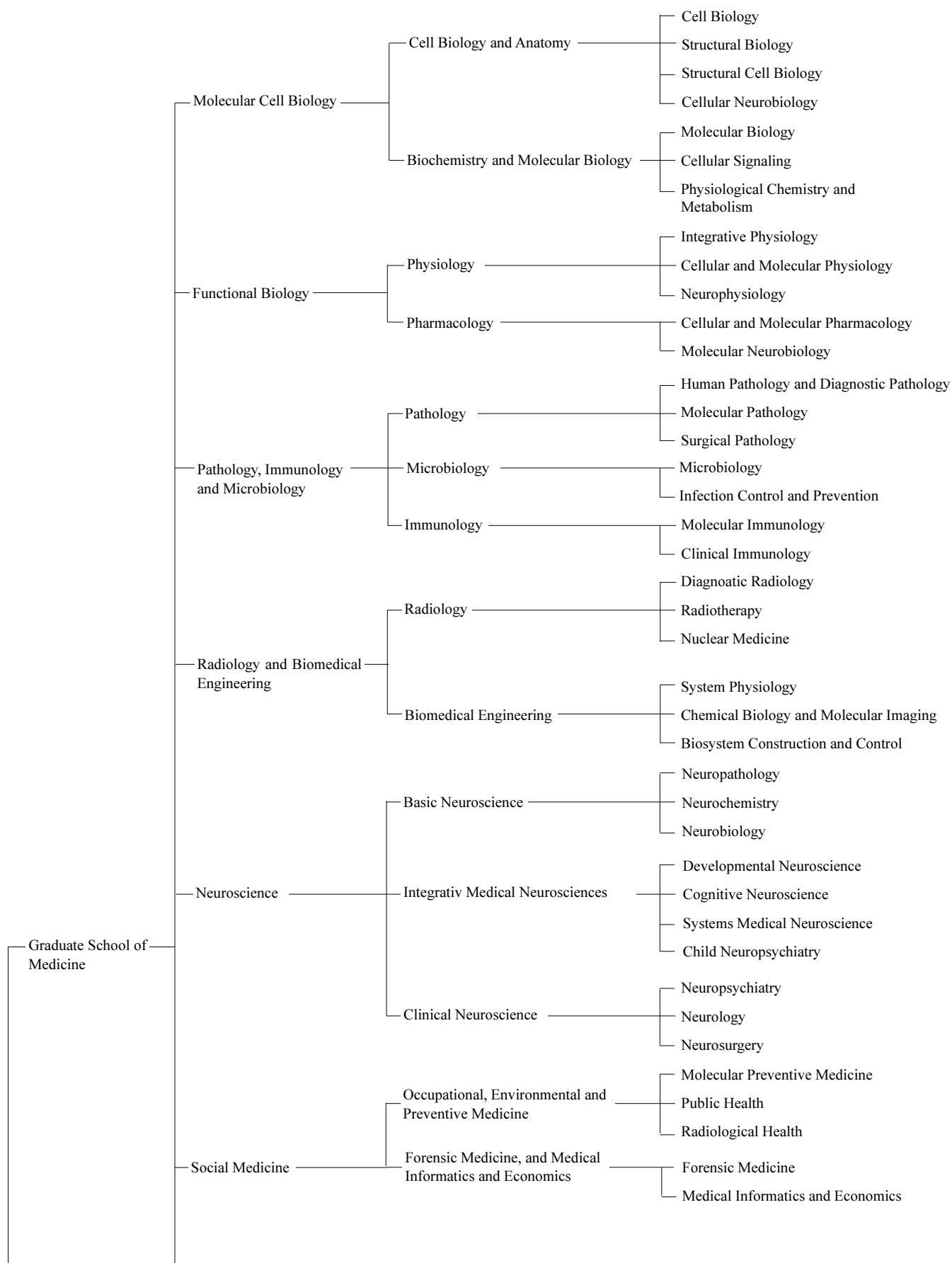
History

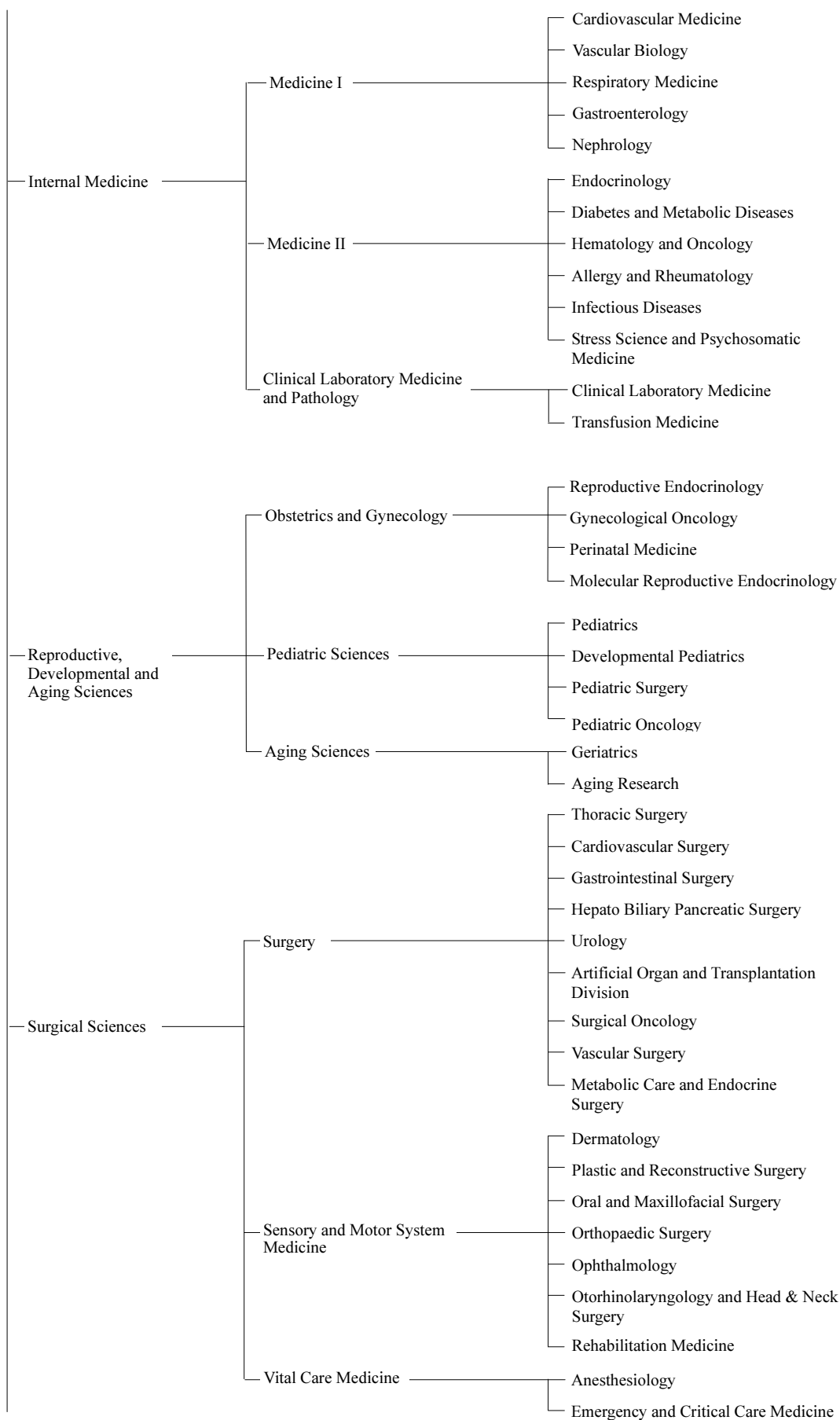
1858	May	Practitioners, trained in Dutch (European) medicine in Edo (Tokyo), laid out money to establish the Shutojo (vaccination center) in Kanda Mitamagaike.
	Nov.	Shutojo was destroyed in a fire that had spread from Kanda Aioicho. Shutojo continued its operations at other sites such as the residence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

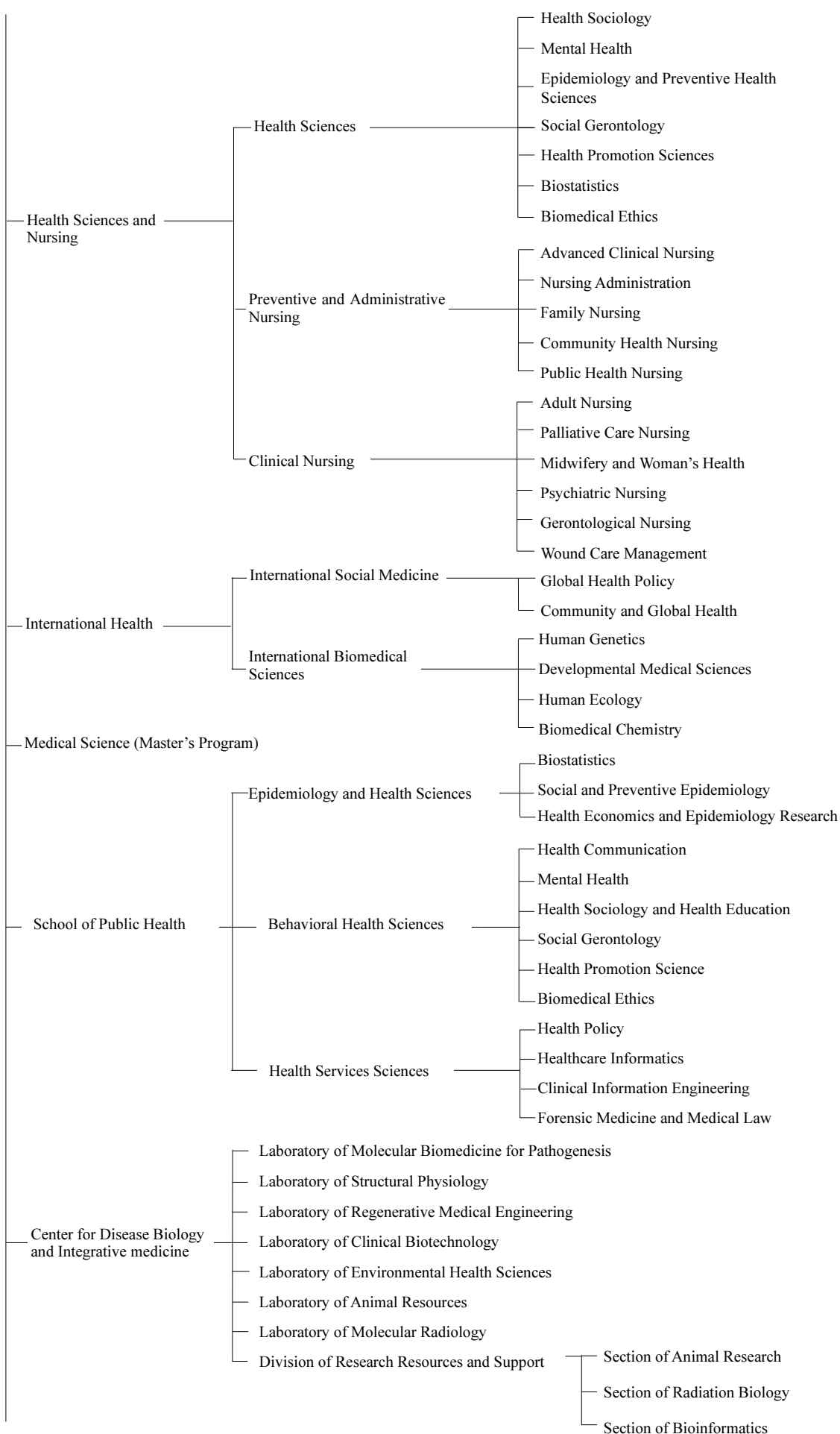
- Jul. The Graduate School was founded, and the Division of Medical Doctor Biological Science was established. The Brain Research Laboratory became the Brain Research Institute of the Faculty of Medicine.
- 1956 Apr. The Midwives School was established.
- 1958 Apr. The Division of Pharmaceutical Sciences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

2000	Apr.	The International Research Center for Medical Education was established (A shared facility for education and research).
2001	Apr.	The University Branch Hospital was united with the University Hospital.
2003	Apr.	The Center for Disease Biology and Integrative Medicine was established.
2004	Apr.	All the National Universities owned by the Japanese Government became National University Corporations. and the University of Corporation.
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.

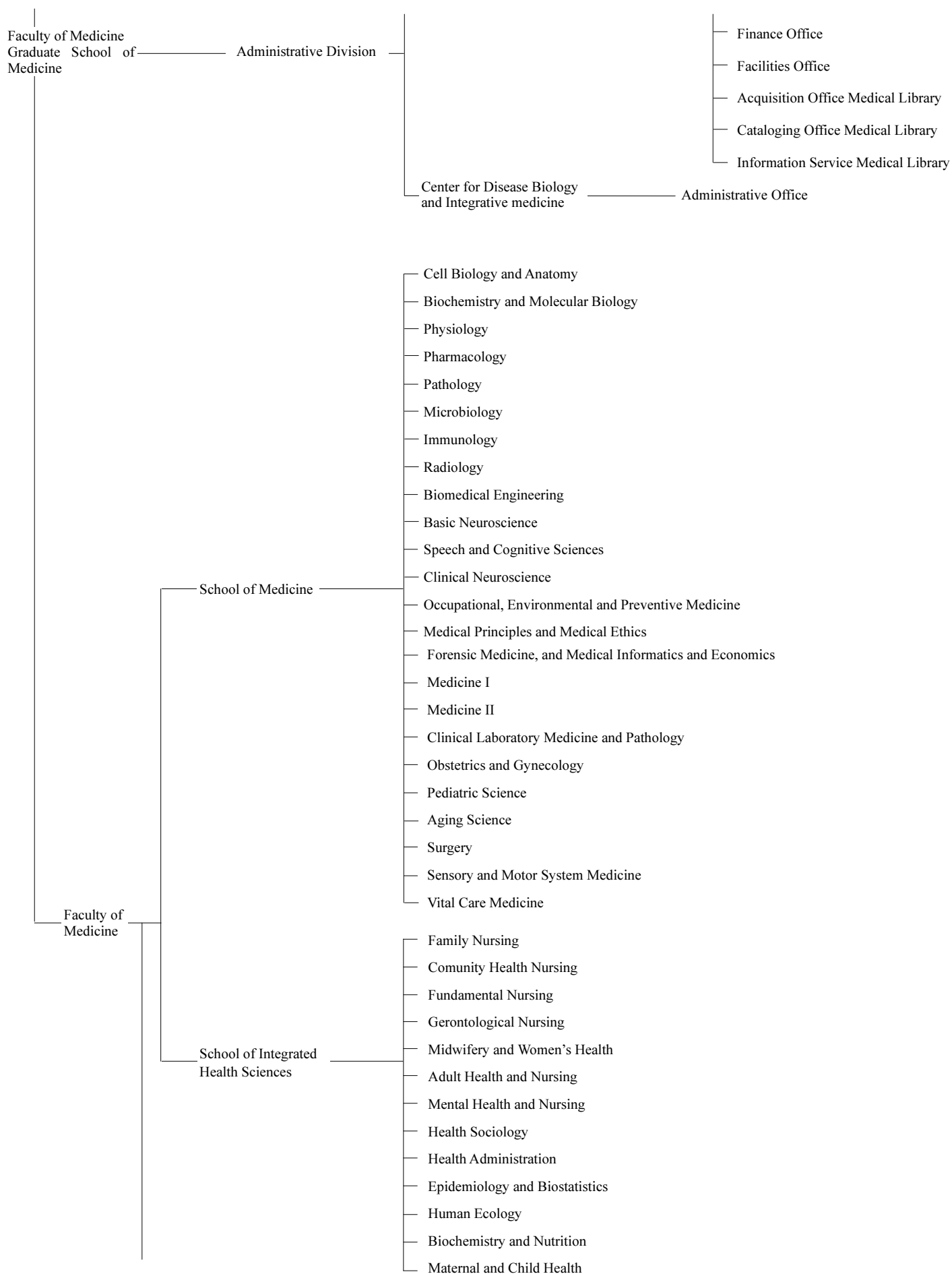
Organization Chart

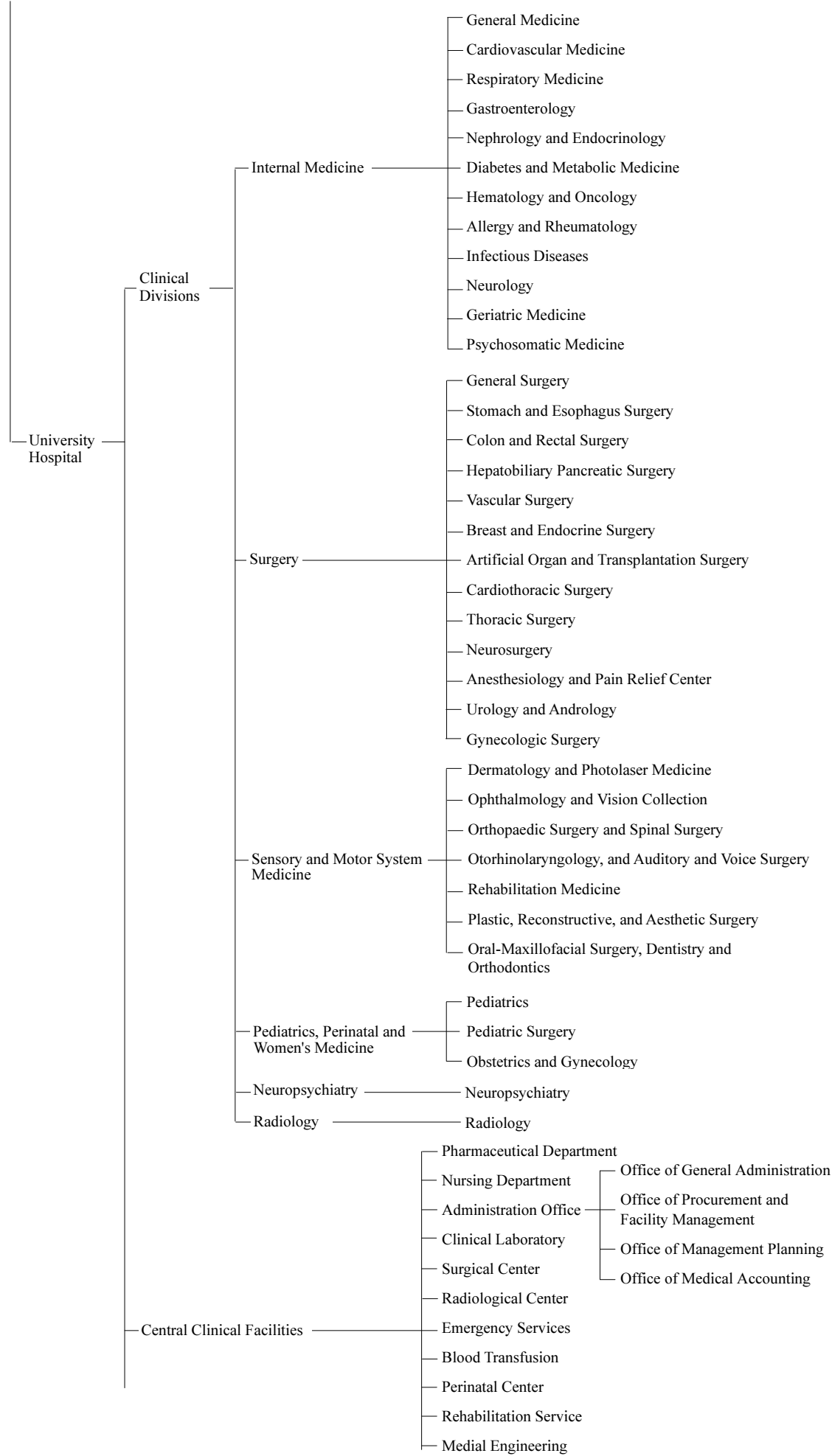


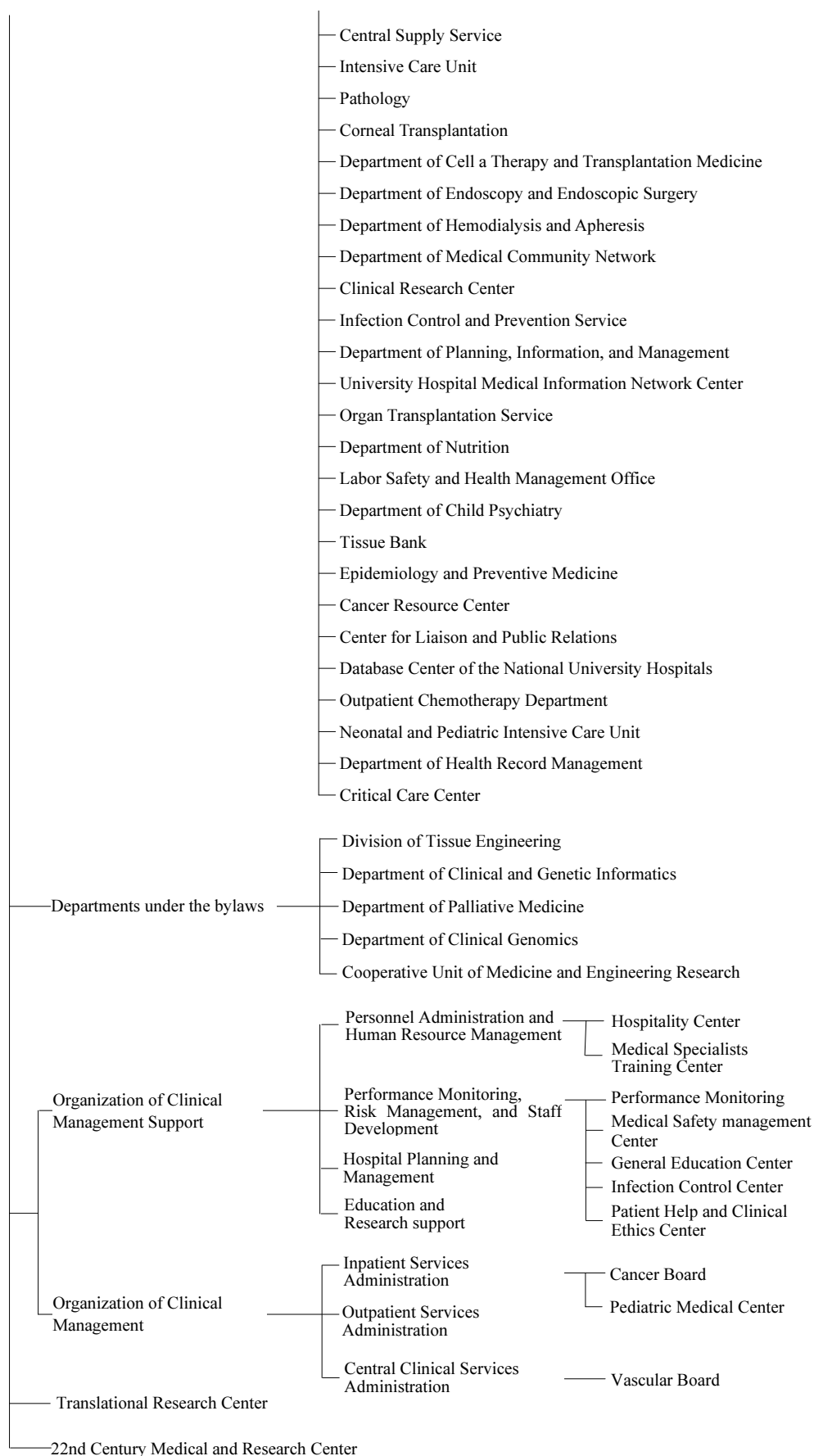












Teaching, Research, Secretarial and Administrative Staffs

Chief Members of Administration

Dean, Graduate School of Medicine (Dean, Faculty of Medicine)		Takao Shimizu
Chairman, School of Health Sciences and Nursing		Kiyoshi kita
Director, Medical Library		Kazuhiko Ohe
Director General, University Hospital		Yuji Taketani
Director, Center for Disease Biology and Integrative Medicine		Masayoshi Mishina
The director of the 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	Hiroto Okayama
	professor	Takao Shimizu
	professor	Hiroki Kurihara

Functional Biology

Department of Physiology	professor	Yasushi Miyashita
	professor	Kensaku Mori
	professor	Masanobu Kano
Department of Pharmacology	professor	Masamitsu Iino
	professor	Masayoshi Mishina

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	Tadatsugu Taniguchi

Radiology and Biomedical Engineering

Department of Radiology	professor	Kuni Otomo
Department of Biomedical Engineering	professor	Yasuteru Urano

Neuroscience

Department of Basic Neuroscience	professor	Takeshi Iwatsubo
	Professor	Kenzo Hirose

Department of Integrative Medical Neuroscience		
Department of Clinical Neuroscience	professor	Kiyoto Kasai
	professor	Shoji Tsuji
	professor	Nobuhito Saito
Social Medicine		
Department of Occupational, Environmental and Preventive Medicine	professor	Koji Matsushima
	professor	Yasuki Kobayashi
Department of Forensic Medicine, and Medical Informatics and Economics	professor	Kenichi Yoshida
	professor	Kazuhiko Ohe
Internal Medicine		
Department of Medicine I	professor	Ryozo Nagai
	professor	Takahide Nagase
	professor	Kazuhiko koike
Department of Medicine II	professor	Toshiro Fujita
	professor	Takashi Kadowaki
	professor	Mineo Kurokawa
	professor	Kazuhiko Yamamoto
	professor	Akira Akabayashi
Department of Clinical Laboratory Medicine and Pathology	professor	Yutaka Yatomi
	professor	Koki Takahashi
Reproductive, Developmental and Aging Science		
Department of Obstetrics and Gynecology	professor	Yuji Taketani
	professor	Shiro Kozuma
Department of Pediatric Science	professor	Takashi Igarashi
	professor	Tadashi Iwanaka
Department of Aging Science	professor	Yasuyoshi Ouchi
Surgical Sciences		
Department of Surgery	professor	Minoru Ono
	professor	Yasuyuki Seto
	professor	Norihiro Kokudo
	professor	Yukio Homma
Department of Sensory and Motor System Medicine	professor	Shinichi Sato
	professor	Isao Koshima
	professor	Tsuyoshi Takato
	Professor	Kozo Nakamura
	professor	Shiro Amano
	professor	Tatsuya Yamasoba
	professor	Nobuhiko Haga

Department of Vital Care Medicine	Professor	Yoshitsugu Yamada
	professor	Naoki Yahagi
Health Sciences and Nursing		
Department of Health Sciences	professor	Norito Kawakami
	professor	Yasuo Ohashi
	professor	Ichiro Kai
	professor	Akira Akabayashi
Department of Preventive and Administrative Nursing	professor	Katsuya Kanda
	professor	Sachiyo Murashima
Department of Clinical Nursing		
	professor	Keiko Kazuma
	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	Kiyoshi Kita
School of Public Health		
Department of Epidemiology and Health Sciences	professor	Yasuo Ohashi
	professor	Satoshi Sasaki
	professor	Hideki Hashimoto
	professor	Takahiro Kiuchi
Department of Behavioral Health Sciences	professor	Norihito Kawakami
	professor	Ichiro Kai
	professor	Akira Akabayashi
Department of Health Services Sciences	professor	Yasuki Kobayashi
	professor	Kazuhiko Ohe
	professor	Hiroshi Oyama
	professor	Kenichi Yoshida

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 Ushida
Laboratory of Clinical Biotechnology	professor	Kazunori Kataoka
Laboratory of Environmental Health Sciences	professor	Chiharu Tohyama
Laboratory of Animal Resources	professor	Atsu Aiba
Laboratory of Molecular Radiology	professor	Kiyoshi Miyakawa
Division of Research Resources and Support		

International Academic Affairs

professor	Tatsuya Yamasoba
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Medical Library

Professor	Kazuhiko Ohe
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Medical Scientist Training Program

Professor	Shigeo Okabe
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Museum of Health and Medicine

Professor	Kazuhiko Ohe
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Faculty of Medicine**Endowed Departments**

Department of Pharmacoepidemiology	professor	Kiyoshi Kubota
Department of Integrated Traditional Medicine(Tsumura)	Associate professor	Tetsuro Okabe
Department of Vascular Regeneration (Daiichi Sankyo Co.,Ltd)	Associate professor	Hiroyuki Koyama
Department of Bone & Cartilage Regenerative Medicine	Associate professor	Taku Saito
Department of Cartilage & Bone Regeneration(Fujisoft)	Associate professor	Kazuto Hoshi
Department of Clinical Renal Regeneration	Associate professor	Keiichi Hishikawa
Department of Metabolome	Professor	Ryo Taguchi
	Associate professor	Yoshiya Oda
Clinical and Molecular Epidemiology (Mitsubishi Tanabe Pharma Corporation.)		
	Associate professor	Takanari Gotoda
Immunotherapeutics (Medinet)	Associate professor	Kazuhiro Kakimi
Total Renal Care Medicine	Associate professor	Akira Ishikawa
Integrated Molecular Science on Metabolic Diseases	Associate professor	Hara Kazuo
Department of Advanced Clinical Science and Therapeutics	Associate professor	Junichi Suzuki
	Associate professor	Yasunobu Hirata
Ischemic Circulatory Physiology, Kaatsu Training	Associate professor	Toshiaki Nakajima
Translational Research for Healthcare and Clinical Science	Associate professor	Hiroyuki Morita
Department of Joint Disease Research	Associate professor	Noriko Yoshimura
Health Management and Policy	Associate professor	Hideo Yasunaga
Computational Diagnostic Radiology and Preventive Medicine	Associate professor	Naoto Hayashi
	Associate professor	Kansei Uno
Clinical Motor System Medicine	Associate professor	Toru Akune
Medical Safety Management (Tokio Marine & Nichido)	Professor	Yasushi Kodama
Molecular Cardiovascular Metabolism	Associate professor	Katsuyuki Ando

The Department of Healthcare Quality Assessment	Associate professor	Hiroaki Miyata
Anti-Aging Medicine	professor	Satoshi Inoue
Integrated Imaging Informatics	Associate professor	Naoki Yoshioka
The Department of Nutriproteomics	professor	Kazumi Yagasaki
Clinical Epidemiology and Systems	professor	Tsutomu Yamazaki
	Associate professor	Daisuke Koide
Clinical Trial Data Manegement	Associate professor	Takuhiro Yamaguchi
Pharmacology and Pharmacokinetics	Associate professor	Akihiro Hisaka
Ubiquitous Preventive Medicine	Associate professor	Toru Suzuki
Science for joint reconstruction	professor	Yoshio Takatori
	Associate professor	Toru Moro
Department of Molecular Research for Vascular Diseases	Associate professor	Daisuke Nagata
Department of Advanced Skin Care (Miss Paris)	professor	Junko Sugama
Department of Therapeutic Strategy for Heart Failure	professor	Shunei Kyo
	Associate professor	Satoshi Gojo
	Associate professor	Takashi Nishimura
Laboratory of Molecular Physiology on Energy Metabolism	Associate professor	Naoya Yahagi
Department of Molecular Neuroscience on Neurodegeneration	Associate professor	Atsushi Iwata
Department of Chronic Kidney Disease	Associate professor	Miki Nagase
Department of Molecular Structure and Dynamics (JEOL/Zeiss)	professor	Nobutaka Hirokawa
Department of Molecular Vascular Endocrinology	Associate professor	Masashi Isshiki
Department of Medical Genomics	professor	Hiroyuki Mano
	Associate professor	Young Lim Choi
Department of Molecular Psychiatry		
Department of Molecular Psychiatry	Associate Professor	Kazuya Iwamoto
Continence medicine	Professor	Yasuhiko Igawa
Department of Life Support Technology (Molten)	Associate Professor	Taketoshi Mori
Quality assessment and control of medical device sterilization	Associate Professor	Yushi Uetera
Social Cooperation Program		
Department of Ubiquitous Health Informatics	Associate Professor	Hideo Fujita
International Research Center for Medical Education		
	Director	Kazuhiko Yamamoto
	professor	Kiyoshi Kitamura
University Hospital		
Clinical Divisions		
General Medicine	Head	Syoji Tsuji
Cardiovascular Medicine	Head	Ryozo Nagai

Respiratory Medicine	Head	Takahide Nagase
Gastroenterology	Head	Kazuhiko Koike
Nephrology and Endocrinology	Head	Toshiro Fujita
Diabetes and Metabolic Medicine	Head	Takashi Kadowaki
Hematology and Oncology	Head	Mineo Kurokawa
Allergy and Rheumatology	Head	Kazuhiko Yamamoto
Infectious Diseases	Head	Hiroshi Yotsuyanagi
Neurology	Head	Shoji Tsuji
Geriatric Medicine	Head	Yasuyosi Ouchi
Psychosomatic Medicine	Head	Akira Akabayashi
General Surgery	Head	Hirokazu Nagawa
Stomach and Esophagus Surgery	Head	Yasuyuki Seto
Colon and Rectal Surgery	Head	Hirokazu Nagawa
Hepatobiliary Pancreatic Surgery	Head	Norihiro Kokudo
Vascular Surgery	Head	Tetsuro Miyata
Breast and Endocrine Surgery	Head	Toshihisa Ogawa
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	Tetsu Yano
Dermatology and Photolaser Medicine	Head	Shinichi Sato
Ophthalmology and Vision Collection	Head	Shiro Amano
Orthopaedic Surgery and Spinal Surgery	Head	Kouzo Nakamura
Otorhinolaryngology and Auditory and Voice Surgery	Head	Tatuya 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	Takashi Igarashi
Pediatric Surgery	Head	Tadashi Iwanaka
Obstetrics and Gynecology	Head	Shiro Kozuma
Neuropsychiatry	Head	Kiyoto Kasai
Radiology	Head	Kuni Ohtomo
Central Clinical Facilities		
Department of Clinical Laboratory	Head	Yutaka Yatomi
Surgical Center	Head	Hiroshi Yasuhara
Radiological Center	Head	Kuni Ohtomo

Emergency Services	Head	Naoki Yahagi
Blood Transfusion	Head	Koki Takahashi
Perinatal Center	Head	Shiro Kozumai
Rehabilitation Service	Head	Nobuhiko Haga
Central Supply Service	Head	Hisayoshi Tamai
Department of Medical Engineering	Head	Kazuhiko Fukatsu
Intensive Care Unit	Head	Naoki Yahagi
Department of Pathology	Head	Masashi Fukayama
Corneal Transplantation	Head	Shiro Amano
Department of Cell Therapy and Transplantation Medicine	Head	Mineo Kurokawa
Department of Endoscopy and Endoscopic Surgery	Head	Mitsuhiro Fujisiro
Center for Hemodialysis and Apheresis	Head	Toshiro Fujita
Medical Community Network	Head	Yasuyoshi Ouchi
Clinical Research Support Center	Head	Takashi Kadowaki
Infection Control and Prevention Service	Head	Kyoji Moriya
Department of Planning, Information and Management	Head	Kazuhiko Ohe
University Hospital Medical Information Network Center	Head	Takahiro Kiuchi
Organ Transplantation Service	Head	Norihiro Kokudo
Department of Child Psychiatry	Head	Yukiko Kano
Tissue Bank	Head	Noboru Motomura
Epidemiology and Preventive Medicine	Head	Tsutomu Yamazaki
Cancer Resource Center	Head	Shoichi Kaisaki
Center for Liaison and Public Relations	Head	Kazuhiko Ohe
Database Center of the National University Hospitals	Head	Hiroshi Kushiya
Outpatient Chemotherapy Department	Head	Norihiro Kokudo
Neonatal and Pediatric Intensive Care Unit	Head	Arata Murakami
Department of Health Record Management	Head	Yasuyoshi Ouchi
Critical Care Center	Head	Susumu Nakajima
Division of Tissue Engineering	Head	Tsuyoshi Takato
Department of Clinical and Genetic Informatics	Head	Ryozo Nagai
Department of Palliative Medicine	Head	Keiichi Nakagawa
Department of Clinical Genomics	Head	Shoji Tsuji
Cooperative Unit of Medicine and Engineering Research	Head	Tetsuro Miyata
Translational Research Center	Head	Ryozo Nagai
22nd Century Medical and Research Center	Head	Kozo Nakamura
Pharmaceutical Department	Head	Hiroshi Suzuki

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., Yosuke Takei, M. D.,

Associate

Yasushi Okada, M. D., Yosuke Tanaka, M. D., Ryo Nitta, M. D.,

Noriko Homma, Ph. D., Harukata Miki, Ph. D.,

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

Teaching activities

Our teaching responsibility is following.

I.

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

II.

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

to medical students and students of other faculties.

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

Research activities

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

Our laboratory studies molecular architecture, dynamics and function of the neuronal cytoskeleton using various new molecular cell biological approaches

including new electron microscopy such as the quick freeze deep etch electron microscopy, 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 elec-

tron microscopy of molecular resolution, biochemistry, biophysics, molecular biology and molecular genetics and X-ray crystallography.

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3. Yin, X., Y. Takei, M. Kido and N. Hirokawa. Molecular motor KIF17 is fundamental for memory and learning via differential support of synaptic NR2A.2B levels. *Neuron* 70; 310-325, 2011

Department of Cell Biology & Anatomy (Structural Biology)

Professor

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

Lecturer

Toshiki Yagi, Ph.D.

Associate

Toshiyuki Oda, 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 includes: Masahide Kikkawa (Professor), Toshiki Yagi (Lecturer), Toshiyuki Oda (Joshu), Toshiharu Sano, Yuma Tani, and Shohei Fujita (student), and Yuka Kimura (secretary).

Teaching activities

Our lab, together with Hirokawa 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

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 observes the frozen samples without staining. Using electron microscopy, we are able to obtain nano-meter resolution of macromolecular complexes such as axonemes. We have been developing new techniques, such as asymmetric helical reconstruction and Ruby-Helix software.

By using these new techniques, we are currently studying dynein-microtubule complex, dynein stalk-microtubule complex to elucidate the mechanism of dynein’s motor functions.

Model Organism

Our lab currently uses *Chlamydomonas* as a model organism for studying flagella. To identify molecules

that are involved in regulating dynein, we use various genetic tools, including classical mutagenesis, siRNA.

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

References

Department of Cellular Neurobiology

Professor

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

Research Associate

Hirohide Iwasaki, Ph.D., Shinji Tanaka, Ph.D.

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

Introduction and Organization

The Department of Cellular Neurobiology 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 25 members.

Teaching activities

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 activities

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. We are investing this subject in vitro and in vivo by visualizing the synaptic molecules and neuronal morphology simultaneously by imaging techniques.

Molecular Cell Biology

2. Biochemistry and Molecular Biology

Department of Molecular Biology

Professor

Hiroto Okayama, M.D., Ph.D.

Associate Professor

Shigeki Jinno, Ph.D.

Associate

Hanako Yamamoto, Ph.D., Shiho Arakawa, Ph.D.

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

Introduction and Organization

This Department was established in 1893 initially as a part of Department of Physiology, but in 1897 became independent. In 1927, it was renamed Department of Biochemistry, in 1974 First Department of Biochemistry and in 1997 Department of Molecular Biology, according to the creation of new related departments and the reorganization of Faculty of Medicine. This Department has been headed by 7 professors, who made great contributions to the development of biochemistry, nutrition and molecular biology in Japan.

Professor Muneo Kumagawa, who headed this first Biochemistry or Medical Chemistry Department established in this country, graduated in 1882 The University of Tokyo Faculty of Medicine. In 1884 he went to Department of Pathology, The University of Berlin headed by Rudolf Virchow and under the supervision of Ernst Salkowski. After returning to Japan, he was promoted to Lecture and 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 was discovered by C. Eijkman in 1906. He educated many including Masahiro Sakaguchi, who developed a world-famous colorimetric method for arginine and Takaoki Sasaki, who first succeeded in generating liver cancer with chemicals.

Professor Samuro Kakiuchi graduated The Imperial University of Tokyo Faculty of Medicine in 1906 and studied under Professor Kumagawa. After studies in US, he come back and succeeded late Kumagawa. He published Journal of Biochemistry and founded the Japanese Society of Biochemistry. His students included Professors Kodama and Shimazono.

Professor Keizo Kodama graduated the Imperial University of Tokyo in 1918. Taking positions of lecturer and Associate Professor and making studies at Cambridge University, he became Professor of Biochemistry Kyushu Imperial University and succeeded Professor Kodama in 1933. He studied oxidation and reduction and nutrition.

Professor Norio Shimazono graduated The Imperial University of Tokyo Faculty of Medicine in 1928, followed by taking positions as associate, lecturer, professor at Niigata Medical School. In 1952 he succeeded Professor Kodama. He studied vitamin B1/cocarcboxylase, ketoacid metabolism and hexose metabolism.

Professor Tamio Yamakawa graduated The Imperial University of Tokyo Faculty of Medicine and began studies at The Institute for Infectious Diseases, The University of Tokyo. After becoming Associate Professor and Professor, he succeeded 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 The

University of Tokyo Faculty of Medicine in 1955. He began studies in Department of Internal Medicine, went to Baylor Collage of Medicine to study under H. Busch, and after coming back, took a position at Cancer Institute and 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 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 P. Berg. Taking a position at NIH US, he became Professor of Molecular Genetics, Osaka University Institute for Infectious Diseases. In 1993 he succeeded Professor Muramatsu. At Stanford and NIH, he studied gene cloning and developed a full length cDNA cloning method and a cDNA expression cloning vector system. After return to Japan, he has been studying cell cycle control and cancer.

Research Activities

Our current study focuses on the understanding of the molecular mechanism enabling the anchorage-independent S phase onset, which is the universal property of cancer cells. All the members of our laboratory are participating in this study.

1. Identification of the intra-cellular pathways mediating signals for cellular anchorage to extra-cellular matrices – the TSC1/TSC2-Rheb-mTORC1 pathway

A key to understand the molecular basis for malignant transformation is elucidation of signal pathways that mediate anchorage signals and control expression and activity of cell cycle start factors including Cdc6 and cyclin A. We have identified that the TSC1/2-Rheb-mTORC1 pathway mediates an anchorage signal and controls Cdk4/Cdk6 activity.

Integrins bound to the extracellular matrix allow GTP-bound Rho A to activate ROCK. Activated ROCK controls assembly of the actin filaments, thereby regulating cell shape and motility. In addition, activated ROCK activates mTORC1 via inactivating Tsc2 by directly

phosphorylating Thr1203. Activated mTORC1 activates Cdk4/Cdk6, which in turn inactivates Rb, and therefore activates E2F, resulting in induction of E2F1 as well as Cdc6 and Cyclin A. Induced E2F1 inactivates the APC/C^{CDH1} ubiquitin ligase, thereby suppressing degradation of Cdc6 and Cyclin A. This finding strongly suggests that the Tsc1/2-Rheb-mTOR cascade serves a major transduction pathway for the anchorage signal to control the G1-S transition. How does mTORC1 control Cdk4/Cdk6 activity? We still do not know the mechanism, but it seems to involve a never anticipated mechanism independent of CKI and cyclin availability.

2. Identification of the intra-cellular pathways mediating signals for cellular anchorage to extra-cellular matrices – the anchorage signal pathway to activate Cdk2

One remaining question regarding the anchorage signal cascade to control the G1-S transition in the cell cycle is: how does anchorage signal regulate Cdk2 activity. When cells traverse G1 phase, Cdk2 is inactivated mainly by p27 until S phase onset. We solved this question. We initially found that when CKI-resistant Cdk6/cyclin D3 complex is overexpressed in anchorage-deprived rat embryonic fibroblasts, Cdk2 remains active at least for initial 36 hr. Detailed analysis revealed the following cascade reactions. Overexpression of Cdk6/cyclin D3 stabilizes Pim1, an oncogene product inactivated by proviral insertion of mouse leukemia virus, and activates ROCK in the absence of anchorage. Activated Pim1 and ROCK phosphorylate the C-terminus of free or Cdk2-bound p27. Cdc6 then activates the Cdk2 by utilizing ATP hydrolysis energy.

Thus, ROCK-mediated C-terminal p27 phosphorylation and subsequent activation of the p27-bound Cdk2 by Cdc6 are the rest of the anchorage signal cascade that regulates the G1-S transition. Consequently, overexpression of Cdk6/cyclin D3, Cdc6 and active Rheb to activate mTORC1 conferred on rat embryonic fibroblasts the ability to proliferate in anchorage-free soft agar medium as rapidly as HeLa, a fully developed human cancer line.

3. New function of Cdc6

We found that Cdc6 has an additional novel function to promote cell proliferation. When cells are deprived of anchorage, they not only arrest in G1 but also suffer cell death known as anoikis, which is executed by caspase-3 activated by FADD –activated caspase-8. But when mTORC1 is activated during anoikis, the apoptosome participates in the activation of caspase-3 because Apaf1 remains expressed during anchorage deprivation while anchorage loss induces mitochondrial permeabilization resulting in release cytochrome C into the cytosol. But when Cdc6 is expressed in anchorage-deprived mTORC1-activated cells, Cdc6 forms a stable complex with cytochrome C-bound Apaf1, thereby blocking caspase-9 activation. This function of Cdc6 is its ATPase-dependent but cyclin-binding motif-independent. Thus, Cdc6 is a tri-functional AAA+ ATPase all working for life. Our finding also provides a clear solution to the paradox that genes essential for proliferation and cell death are regulated at the same time and by the same E2F transcription factor.

Education

To medical students, we give lectures on DNA and related. DNA replication, transcription, nuclear export of mRNA, translation, gene engineering, mobile DNA and metabolism of nucleic acids are the topics covered by the lectures. To graduate course students, the genetic engineering course consisting of lectures and experiments is provided.

Publication

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Department of Cellular Signaling

Professor

Takao Shimizu, M.D., Ph.D.

Associate Professor

Motono Nakamura, Ph.D.

Research Associate

Yoshihiro Kita, Ph.D., Hideo Shindou, Ph.D., Keisuke Yanagida, Ph.D.

Homepage <http://biochem2.umin.jp/index.html>

Introduction and Organization

In addition to the above 5 faculty members, we have 8 graduate students (7 doctor course students and 1 master course student), and 8 undergraduate medical students (Free Quarter and others). Three postdoc scientists and several clinical researchers are also our members. We have two foreign scientists (one postdoc from Germany and one graduate student from Taiwan). Ms. Toshie Takahashi (Assistant belongs to the Dean of the Faculty), Ms. Fumie Hamano (Research associate) and Mr. Shinji Ichihara (Technical staff) are in charge of maintenance and education of various instruments for common use. Professor Takao Shimizu has been awarded Japan Academy Prize in June 2009.

Education

For about 100 undergraduate students from the Faculty of Medicine, and about 5 students from Faculty of Science (Department of Anthropology), we deliver about 80 lectures, small-group seminars, and laboratory course for a couple of weeks. Our laboratory is accepting Free Quarter students every year, and the total number from 2003 to 2010 is over 25. For graduate course students, we have three-month lecture series and one-week practical training (Lecture on receptor and signal transduction), and an eight-week laboratory course for clinical

scientists.

Research

1. Lipid mediator and lipid metabolism.

Oxygenated products of arachidonic acid (prostaglandins, leukotrienes, and hydroxyeicosatetraenoic acids) as well as bioactive phospholipids (platelet-activating factor and other related phospholipids) activate cellular signaling pathways in various cells. These lipid mediators, working together with other bioactive substances such as neurotransmitters and cytokines, are now considered to play significant roles in neuronal plasticity and self-defense systems. To identify the roles of lipid mediators in the living systems, principally three approaches are ongoing with different strategies; (1) isolation of enzymes involved in syntheses and degradation of lipid mediators, cloning of cDNAs and genes, elucidation of enzyme regulation at transcriptional and posttranscriptional levels; (2) cloning of G-protein coupled receptors for lipid mediators and clarification of intracellular trafficking and signaling mechanisms; and (3) target disruption or overexpression of the gene of interest in mice, and identification of the *in vivo* role of each molecule by examining phenotypes of these mice. In the last several years we have cloned several key enzymes of phospholipid metabolism and receptors for lipid mediators. Recently, we have successfully

identified several lysophospholipid acyltransferases involving in Lands' cycle. Thus, we are able to explain the molecular mechanism and biological significance of diversity and asymmetry of membrane lipids. Several lines of transgenic mice and knock-out mice were established and their phenotypes were analyzed. We found that these mediators are involved in inflammation, allergy, and neuronal functions.

2. Simultaneous quantitation of lipid mediators.

Lipid mediators are produced through a cascade pathway. In the cascade known as "arachidonate cascade", several key enzymes such as cytosolic phospholipase A2, cyclooxygenases, and lipoxygenases function as common regulators in combination with various terminal synthases that produce specific lipid mediator molecular species. For a comprehensive analysis of lipid mediators, a simultaneous quantitation method with sensitivity and reliability is necessary. Thus, we have recently developed a quantitation system for multiplex lipid mediators by column-switching HPLC–tandem mass spectrometry. When optimized, the system enables the rapid analysis of 14 lipid mediators with a throughput of 96 samples/24 h, lower limits of quantitation of 5 pg on column, and linear calibration ranges up to 2,000–5,000 pg. Indeed, we successfully detected dynamic changes in a series of lipid mediators in some pathologic tissues of rodents.

3. Various instrumental analyses.

The Faculty of Medicine has various analytical and preparative instruments for the common use, which include mass spectrometers (LCMS-IT-TOF, AXIMA, Performance [Shimadzu], Exactive, TSQ 7000, TSQ Quantum Ultra, LCQ [Thermo Fischer], Q-TOF micro [Waters], Q-TOF micro [JASCO], and 4000 Q TRAP [AB Sciex]) equipped with gas chromatographs or HPLC, PerkinElmer peptide sequencers, FUJI BAS 2000 image analyzer, BD FACScan, and Beckman capillary electrophoresis system (P/ACE 2000). Ms. Takahashi is in charge of the maintenance of these machines and instruction for the beginners. As her own projects, she is identifying peptide sequences of various proteins by HPLC-MS, and identification of small-molecular

weight compounds by GC-MS and HPLC-MS.

4. Internet Web site

To see our research activities in more detail, please refer to our web site (http://biochem2.umin.jp/index_j.html). In this homepage, you will also find our experimental protocol useful for the molecular and cellular biology studies. Dr. Kita and Mr Harayama are in charge of the homepage.

5. Collaboration with Department of Metabolome and Department of Lipidomics

Department of Metabolome (2003-2011) and Department of Lipidomics (2011-present) have been established by the donation of Shimadzu Co., Ltd, and Ono Pharmaceutical Co. In collaboration with them, we are searching for novel lipid mediators that bind to orphan G-protein-coupled receptors, lacking identified cognate ligands. In this collaboration we recently determined 12HHT (12(S)-Hydroxyheptadeca-5Z,8E,10E-trienoic acid) as a novel ligand for BLT2 which has been recognized as the low affinity second LTB₄ receptor. We also succeeded in molecular cloning of lung-type acyl-coa:lysophosphatidylcholine acyltransferase 1 (LPCAT1) involving in production of lung surfactant. These research are supported by Grant-in-Aids from the Ministry of Education, Culture, Sports, Science, and Technology of Japan, the Ministry of Health, Labour, and Welfare of Japan (Health and Labour Sciences Research Grants), Nanobio Integration Program of the University of Tokyo, and a global COE program.

Publications

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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, 6 graduate students, 2 technical staffs and 1 secretary.

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.

Research Activities

1. Developmental Biology and Medicine

(1) Neural crest and craniofacial development

We have investigated the role of endothelin-1 (ET-1) signaling in neural crest and craniofacial development and identified the ET-1/ETA-receptor to *Dlx5/6* pathway in the dorsoventral axis patterning of crest-driven branchial arch structures. To further clarify the underlying mechanism, we have established mice in which gene cassettes can be efficiently knocked-in into the *Ednra* locus using recombinase-mediated cassette exchange (RMCE) based on the *Cre-lox* system. Using this system, we have demonstrated that the dorsoventral axis patterning of pharyngeal arches is regulated by the ETA-receptor-selective, G_q/G_{11} -dependent signaling, while the formation of the distal pharyngeal region is under the control of a G_q/G_{11} -independent signaling. We also identified Calpain6 as a downstream molecule of the ET-1 pathway and its biological function in cytoskeletal organization and cell motility. We further identified TAZ as a protein that binds to and coactivates Pax3, a key transcription factor in neural crest development and

its role in the organogenesis of the kidney and lung as revealed by gene knockout.

(2) Preimplantation development

We characterized the role of sirtuins, NAD⁺-dependent protein deacetylases, in mouse preimplantation development under in vitro culture conditions. Among all sirtuins (Sirt1-7), which are expressed in eggs and early embryos, Sirt3 proved to play a protective role against oxidative stress during preimplantation development. Sirt3 inactivation increased mitochondrial ROS production, leading to the upregulation of p53 and changes in downstream gene expression. p53 inactivation improved developmental outcome of Sirt3-knockdown embryos, indicating that the ROS-p53 pathway is responsible for the developmental defects. These findings may contribute to the understanding of preimplantation biology and give a clue to the better outcome of assisted reproductive technologies.

(3) Angiogenesis

We found that Id1 confers in vivo angiogenic property to human vascular endothelial cells via angiopoietin-1 upregulation, which may give a clue to novel strategy for therapeutic angiogenesis. We also found that the function of Id1 is controlled by protein kinase A through nucleoplasmic shuttling.

2. Mouse Genetics

Collaborative works as follows are going on by using gene manipulation approach in mice.

- (1) Physiological roles of vasoactive peptides
- (2) Pathophysiological roles of defensin
- (3) Developmental roles of non-coding RNA

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Functional Biology

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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 (Drs. A. Nambu, S. Kaname, S. Sugiura and Y. Shibagaki) 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*, and 4 students (M0, M1 and M4) continued to enjoy their researches from 2010 through 2011. 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 Psychology in Faculty of Letters and Department of Biophysics in Faculty of Science. As part of a teaching activity for the graduate students, we have another weekly English seminar, in

which the graduate students learn how to give presentations and hold discussions and debates in English.

Research activities

Most of our research is focused on the higher brain function of the mammalian central nervous system : (1) higher functions of vision and memory, (2) non-invasive measurements of human brain activities and (3) non-invasive functional measurements of monkey brain activities that links above (1) and (2). The results of such research have been published in first-rate journals, as listed in the reference. A brief summary of each topic follows:

- (1) In the primate, visual information processing in the cerebral cortex proceeds along the neural pathway originating from the primary visual area in the occipital lobe to the anterior part of the temporal association cortex. Our laboratory discovered several classes of important *memory-neurons* electrophysiologically in the temporal lobe of the monkey. In the inferotemporal cortex, which we propose to be the storehouse of visual long-term memory, we discovered a group of neurons which encode object-object association. We found that the backward signal from the medial temporal lobe to the inferotemporal cortex mediates formation of the mnemonic neural circuits for the association. Recently we also found that the top-down signal from the prefrontal cortex to the inferotemporal cortex plays a central role in retrieval of the mnemonic associative neural code stored in the inferotemporal cortex. Since *association* is a basic mechanism for constructing the human memory-based knowledge system, our finding provides a key to understanding the basic organization of the primate cerebral cortex.
- (2) The recent explosion of new technologies for noninvasive measurements of human brain activities, especially of functional magnetic resonance imaging (fMRI), allows us to observe parallel activation of functional brain modules in humans engaged in various mental tasks. We contributed to development of a new method called “event-related fMRI”, which enables to

utilize the time resolution of fMRI. We applied this “event-related fMRI” method to the analysis of human cognition, and identified several functional centers in the human prefrontal cortex in cognitive tasks such as the Wisconsin Card Sorting Task.

- (3) Recently, we successfully applied fMRI method to macaque monkeys performing highly intelligent cognitive *tasks*. These fMRI studies were done in ultra-high field MRI scanner at 4.7 Tesla, successfully providing much higher spatial resolution than in a conventional clinical MRI scanner. This approach provides us a new approach that bridges a gap between the human non-invasive studies and the various invasive studies in animals, including intra-cortical electrical microstimulation and reversible functional inactivation with GABA agonist drug injections.

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Introduction

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

The present members include the above stuffs, 3 postdoctoral researchers, 2 visiting scientist, 8 graduate students and 1 secretary stuff.

Education

The department provides lectures and practice in physiology for undergraduate students. We teach electrophysiological methods 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 sensory physiology and molecular and cellular neurobiology. Seminars, progress reports, and journal club for graduate students are routinely provided. Monthly joint seminars (Functional Biology Seminars and RIKEN BSI Group Seminars) are also provided for graduate students.

Research

Using multidisciplinary approaches including electrophysiology, optical imaging, molecular and cellular biology and molecular genetics, we at the Department of Cellular and Molecular Physiology aim at understanding neuronal circuit mechanisms for the translation of olfactory sensory inputs to a variety of behavioral and emotional outputs in the mammalian brain. Our recent focus includes the functional and spatial organization of the odor maps in the olfactory bulb, axonal projection pattern of olfactory bulb neurons to various areas of the olfactory cortex, and olfactory cortical mechanisms for the recognition of objects. We study also behavioral state-dependent change in the information processing mode in the olfactory bulb and olfactory cortex, focusing on the experience-dependent reorganization of neuronal circuitry in the olfactory cortex and bulb during postprandial slow-wave sleep.

Granule cells in the olfactory bulb continue to be generated in adulthood, with nearly half incorporated and remainder eliminated into or from the neuronal circuit of the olfactory bulb. We have been investigating the neuronal mechanisms during olfactory experience and those during postprandial sleep for the sensory-experience dependent

incorporation and/or elimination of adult-born granule cells into or from the pre-existing neuronal circuit in the olfactory bulb.

Currently we are focusing on the following topics.

- (1) Analysis of the functional neuronal circuits in the central olfactory system.

Based on the knowledge of the ‘odorant receptor maps’ and ‘functional compartmentalization in the odor map’ in the olfactory bulb, we are studying the manner of olfactory information processing in the olfactory bulb, olfactory cortex and higher olfactory association regions.

The glomerular layer of the mammalian olfactory bulb forms odorant receptor maps. Each map is structurally and functionally compartmentalized into zones (dorsal and ventral) and domains (DI and DII). We previously reported that glomeruli with similar molecular receptive range properties formed molecular feature clusters at stereotypical positions in the rat olfactory bulb. However the spatial arrangement of the molecular feature clusters with regard to the zones and domains has not been systematically examined. We optically mapped the molecular feature clusters of glomeruli within the domain and zone framework of the olfactory bulb using domain-visible class II GFP transgenic mice. In all mice examined, fatty acid-responsive cluster A was located in the lateral part of domain DI, whereas clusters B, C, and D were arranged in an anterior to posterior order within domain DII. These results show that molecular feature clusters correspond to specific subsets of glomeruli in selective domains of the odorant receptor map, suggesting that the molecular feature clusters represent specific odorant receptors that have similar molecular receptive range properties and functional roles.

By combining the methods of optical imaging of intrinsic signals to identify the glomeruli that respond to fox odor trimethylthiazoline (TMT), the electrophysiological single-neuron recording

from individual TMT-responsive mitral cells or tufted cells, and juxtacellular single cell labeling methods, we traced the entire axons of the labeled mitral and tufted cells in various areas of the olfactory cortex.

Rodents can localize odor sources by comparing inputs to the right and left nostrils. However, the neuronal circuits underlying such odor localization are not known. We recorded neurons in the anterior olfactory nucleus (AON) while administering odors to the ipsilateral or contralateral (ipsi- or contra-) nostril. Neurons in the AON pars externa (AONpE) showed respiration phase-locked excitatory spike responses to ipsinostril-only stimulation with a category of odorants, and inhibitory responses to contranostril-only stimulation with the same odorants. Simultaneous odor stimulation of the ipsi- and contranostrils elicited significantly smaller responses than ipsinostril-only stimulation, indicating that AONpE neurons subtract the contranostril odor inputs from ipsinostril odor inputs. An ipsilateral odor source induced larger responses than a centrally located source, whereas an odor source at the contralateral position elicited inhibitory responses. These results indicate that individual AONpE neurons can distinguish the right or left position of an odor source by referencing signals from the two nostrils.

- (2) Reorganization of olfactory neuronal circuits during slow-wave sleep

The olfactory cortex is functionally isolated from the external odor world during slow-wave sleep. However, the neuronal activity pattern in the olfactory cortex and its functional roles during slow-wave sleep are not well understood. We demonstrate in freely behaving rats that the anterior piriform cortex, a major area of the olfactory cortex, repeatedly generates sharp waves that are accompanied by synchronized discharges of numerous cortical neurons. Olfactory cortex sharp waves occurred relatively independently of hippocampal sharp waves. Current source density analysis showed that sharp wave generation

involved the participation of recurrent association fiber synapses to pyramidal cells in the olfactory cortex. During slow wave sleep, the olfactory bulb showed sharp waves that were in synchrony with olfactory cortex sharp waves, indicating that olfactory cortex drove synchronized top-down inputs to the olfactory bulb. Based on these results, we speculate that the olfactory cortex sharp waves may play a role in the reorganization of bulbar neuronal circuits during slow-wave sleep.

(3) Incorporation of adult-born interneurons in the pre-existing neuronal circuit in the olfactory bulb.

The olfactory system is chosen as a model system with which to study the recruitment of newly-generated neurons in the adult neuronal circuit. We are studying cellular and molecular mechanisms that segregate the fate of new neurons between successful incorporation and apoptotic elimination into/from the neuronal circuit. Recently we noted that the elimination of newly-generated granule cells in the olfactory bulb is greatly enhanced during the specific time window of postprandial sleep. Sensory experience-dependent enhancement of granule cell elimination also occurred during postprandial rest/sleep period. These results suggest that extensive structural reorganization of bulbar circuitry occurs during the postprandial period, reflecting sensory experience during preceding waking period.

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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 3 faculty members (professor, associate professor, associate), 6 postdoctoral fellows, 7 graduate students, 1 undergraduate and 4 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. 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 end-plate 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, and Laboratory 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

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Introduction and Organization

Our department was founded in 1885 and collaborates with the Department of Molecular Neurobiology and 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 eight 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 ($[\text{Ca}^{2+}]_i$), or Ca^{2+} oscillation. Many cellular functions are regulated by the Ca^{2+} oscillation frequency. However, fundamental questions remain. How and why does $[\text{Ca}^{2+}]_i$ 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

IP₃R indeed plays an essential role in regulating the Ca²⁺ signal dynamics including Ca²⁺ oscillation.

In order to further study the mechanism underlying Ca²⁺ oscillation, we visualized the Ca²⁺ concentrations within the intracellular organelles (both endoplasmic reticulum and mitochondria) during Ca²⁺ oscillations. We found that Ca²⁺ shuttles between these intracellular organelles in phase with cytoplasmic Ca²⁺ oscillations. Our results also indicated that the Ca²⁺ shuttling determines the Ca²⁺ oscillation frequency. Thus, we have shown that mitochondria play an important role in the generation of Ca²⁺ oscillation. These results provide a clue to the mechanism of Ca²⁺ oscillation.

Why then does [Ca²⁺]_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 Ca²⁺ oscillation frequency. NFAT is dephosphorylated by Ca²⁺-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 [Ca²⁺]_i. With increasing frequency of Ca²⁺ oscillation, dephosphorylated NFAT accumulates in the cytoplasm to enhance its nuclear translocation. This is the molecular basis of the mechanism that decodes the Ca²⁺ oscillation frequency. We also showed that Ca²⁺ oscillation is more cost-effective in regulating cell functions than a continuous increase in Ca²⁺. These studies provide us with an insight into the secrets of Ca²⁺ signalling.

2) Imaging of signalling molecules

Our study on Ca²⁺ 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 Ca²⁺ signals. We have succeeded in imaging IP₃ 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 from 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 new cellular functions that are regulated by Ca²⁺ signals

Although many important cell functions have been found to be regulated by Ca²⁺ signals, not all the Ca²⁺-dependent cell functions have been identified. We are now searching for new cell functions that are regulated by Ca²⁺ 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 $\text{IP}_3\text{-Ca}^{2+}$ 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 $\text{IP}_3\text{-Ca}^{2+}$ 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. We are now studying the molecular mechanism that links between Ca^{2+} signals and N-cadherin expression. Furthermore, we recently showed that $\text{IP}_3\text{-Ca}^{2+}$ signaling in cerebellar astrocytes (Bergmann glia) regulates glutamate transporter levels in Bergman glial cells to maintain glutamate clearance in the mature cerebellum.

4) Cell-to-cell variability in Ca^{2+} signals

Cell-to-cell phenotypic variability within clonal populations has attracted considerable attention. We found that human embryonic kidney 293 cells exhibit all-or-none phenotypic variability in Ca^{2+} response upon agonist application: only approximately 40% of the cells respond to caffeine. Using a systems-biological approach that

combines time-lapse Ca^{2+} imaging and mathematical modeling, we analyzing the basis of the cell-to-cell variability. We found that the balance between Ca^{2+} release and uptake is enhanced by the positive feedback property of the Ca^{2+} release to generate the all-or-none property of the Ca^{2+} release. Furthermore, individual cells switched between the caffeine-sensitive and caffeine-insensitive states with an average transition time of approximately 65 h, suggestive of temporal fluctuation in endogenous protein expression levels associated with caffeine response. Thus, the study provides a conceptual basis of the cell-to-cell phenotypic variability in mammalian cells.

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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 41 lectures per year including those given by seven invited lectures to cover specialized and currently highlighted fields in pharmacology. We offer several laboratory courses, and all the members of the Department participate in the courses to provide close consultation for the students.

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

Research activities

Current research activities are focused on the molecular mechanism and regulation of learning and memory. Brain function is based on highly complex neural networks and their dynamics. The glutamate receptor (GluR) plays a key role in brain dynamics. We elucidated the diversity of the NMDA-type GluR

by molecular cloning and functional expression. Ablation of the NMDA receptor GluR ϵ 1 (GluN2A) by gene targeting resulted in the increase of thresholds for both hippocampal long-term potentiation (LTP) induction and contextual learning. Furthermore, cerebellar Purkinje cell (PC)-specific GluR δ 2 (GluD2) mutant mice showed impairment of cerebellar long-term depression (LTD) and motor learning. These results suggest that GluR is a key molecule of learning and memory. We found Delphilin as a GluR δ 2-interacting molecule, which showed selective expression in cerebellar PCs similar to GluR δ 2. Ablation of Delphilin facilitated LTD induction at parallel fiber (PF)-PC synapses and enhanced optokinetic response (OKR) gain-increase adaptation without affecting any detectable histological abnormalities. This finding suggests that LTD induction at PF-PC synapses is a crucial rate-limiting step for OKR adaptation, a simple form of motor learning. Further analyses of GluR δ 2 and GluR ϵ 1 mutant mice revealed that the temporal relationship of conditioned and unconditioned stimuli determines the neural substrates of eyeblink conditioning, a simple form of associate learning, implying a systemic regulation of learning and memory.

To investigate the regulation of learning and memory, we established an inducible and

neuron-specific gene targeting system on the pure C57BL/6 genetic background by employing Cre-progesterone receptor fusion recombinase (CrePR) for temporal regulation of gene targeting and Flp/rtt recombination system for elimination of marker genes. Since brain functions are the products of dynamic interactions between multiple genes and environments, it is crucial to manipulate genes on the same and homogenous genetic background and then to analyze and compare the phenotypes of various genetically modified mice.

Fear is one of the most potent emotional experiences and is an adaptive component of response to potentially threatening stimuli. On the other hand, too much or inappropriate fear accounts for many common psychiatric problems. Cumulative evidence suggests that the amygdala plays a central role in the acquisition, storage and expression of fear memory. We developed an inducible striatal neuron ablation system in transgenic mice. The ablation of striatal neurons hardly affected the auditory fear learning under the standard condition in agreement with previous studies. When conditioned with a low-intensity unconditioned stimulus, however, the formation of long-term fear memory but not short-term memory was impaired in striatal neuron-ablated mice. Consistently, the ablation of striatal neurons 24 h after conditioning with the low-intensity unconditioned stimulus, when the long-term fear memory was formed, diminished the retention of the long-term memory. Our results reveal a novel form of the auditory fear memory depending on striatal neurons at the low-intensity unconditioned stimulus.

Synchronized discharges in the hippocampal CA3 recurrent network are supposed to underlie network oscillations, memory formation and seizure generation. In the hippocampal CA3 network, NMDA receptors are abundant at the recurrent synapses but scarce at the mossy fiber synapses. We generated mutant mice in which NMDA receptors were abolished in hippocampal CA3 pyramidal neurons by postnatal day 14. We found that mutant mice lacking NMDA receptors selectively in CA3 pyramidal neurons became more susceptible to kainate-induced seizures. Consistently, mutant mice showed characteristic large EEG spikes associated with multiple unit activities (MUA), suggesting enhanced synchronous firing of

CA3 neurons. The electrophysiological balance between fast excitatory and inhibitory synaptic transmission was comparable between control and mutant pyramidal neurons in the hippocampal CA3 region, while the NMDA receptor-slow AHP coupling was diminished in the mutant neurons. In the adult brain, inducible ablation of NMDA receptors in the hippocampal CA3 region by the viral expression vector for Cre recombinase also induced similar large EEG spikes. Furthermore, pharmacological blockade of CA3 NMDA receptors enhanced the susceptibility to kainate-induced seizures. These results raise an intriguing possibility that hippocampal CA3 NMDA receptors may suppress the excitability of the recurrent network as a whole *in vivo* by restricting synchronous firing of CA3 neurons

Interestingly, the NMDA receptor GluR ϵ 2 (GluN2B) was essential for formation of the whisker-related neuronal barrelette structure in the brainstem trigeminal nucleus. The number of PF-PC synapses was decreased in GluR δ 2 mutant mice and multiple climbing fiber innervation was sustained. These observations led to a working hypothesis that memory formation in the adult brain and synapse refinement during development may share common molecular mechanisms.

We then examined the role of GluR δ 2 in the adult brain by inducible and cerebellar PC-specific gene targeting. Concomitant with the decrease of postsynaptic GluR δ 2 proteins, presynaptic active zones shrank progressively and postsynaptic density (PSD) expanded, resulting in mismatching between pre- and postsynaptic specializations at PF-PC synapses. Furthermore, GluR δ 2 and PSD-93 proteins were concentrated at the contacted portion of mismatched synapses, while α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors distributed in both the contacted and dissociated portions. When GluR δ 2 proteins were diminished, PC spines lost their synaptic contacts. We thus identified postsynaptic GluR δ 2 as a key regulator of the presynaptic active zone and PSD organization at PF-PC synapses in the adult brain. Possibly, the postsynaptic GluR δ 2 complex makes a physical linkage between the active zone and PSD to ensure the pre- and postsynaptic matching. These observations support the notion that

there is a common molecular mechanism underlying synaptic plasticity and synapse formation.

GluR δ 2 selectively expressed in cerebellar PCs plays key roles in LTD induction at PF-PC synapses, motor learning, the matching and connection of PF-PC synapses in developing and adult cerebella, the elimination of multiple climbing fibers (CFs) during development and the regulation of CF territory on PCs. However, it remains unsolved how GluR δ 2 regulates cerebellar synaptic plasticity, PF-PC synapse formation and CF wiring. One possible signaling mechanism through GluR δ 2 is signaling by protein-protein interactions. The carboxyl-terminal region of GluR δ 2 contains at least three domains for protein-protein interactions. The PDZ-binding domain at the carboxyl terminal, named as the T site, interacts with several PSD proteins. We generated GluR δ 2 Δ T mice carrying mutant GluR δ 2 lacking the T site. There were no significant differences in the amount of receptor proteins at synapses, histological features and the fine structures of PF-PC synapses between wild-type and GluR δ 2 Δ T mice. However, LTD induction at PF-PC synapses and improvement in the accelerating rotarod test were impaired in GluR δ 2 Δ T mice. Furthermore, CF territory expanded distally and ectopic innervation of CFs occurred at distal dendrites in GluR δ 2 Δ T mice, but the elimination of surplus CF innervation at proximal dendrites appeared to proceed normally. These results suggest that the carboxyl-terminal T site of GluR δ 2 is essential for LTD induction and the regulation of CF territory, but is dispensable for PF-PC synapse formation and the elimination of surplus CFs at proximal dendrites during development.

We propose that GluR δ 2 regulates synapse formation by making a physical linkage between the active zone and postsynaptic density. To examine the issue, GluR δ 2-transfected 293T cells were cultured with cerebellar neurons. We found numerous punctate signals for presynaptic markers on the surface of 293T cells expressing GluR δ 2. The presynaptic specializations induced by GluR δ 2 were capable of exo- and endocytosis as indicated by FM1-43 dye labeling. Replacement of the extracellular N-terminal domain (NTD) of GluR δ 2 with that of the AMPA receptor GluR α 1 abolished the inducing activity. The NTD of GluR δ 2 fused to the immunoglobulin constant

region successfully induced the accumulation of presynaptic specializations on the surface of beads bearing the fusion protein. These results suggest that GluR δ 2 triggers presynaptic differentiation by direct interaction with presynaptic components through the NTD.

To investigate the molecular mechanism of synapse formation, we developed neuron-specific gene manipulations in transparent zebrafish embryos. Transparent zebrafish embryos enable us to visualize synapse formation *in vivo*. Synaptic vesicle accumulation and morphological changes are characteristic features of axon terminal differentiation during synaptogenesis. To investigate the regulatory mechanism that orchestrates synaptic molecules to form mature presynaptic terminals, we visualized a single axon terminal of zebrafish olfactory sensory neurons *in vivo* and examined the effects of the neuron-specific gene manipulations on the axon terminal differentiation. Synaptic vesicles visualized with vesicle-associated membrane protein 2 (VAMP2)-enhanced green fluorescent protein (EGFP) fusion protein gradually accumulated in axon terminals, while the axon terminals visualized with GAP43 fused with EGFP remodeled from complex shapes with filopodia to simple shapes without filopodia from 50 hours postfertilization (hpf) to 84 hpf.

Expression of dominant-negative protein kinase A (PKA) or cAMP response element binding protein (CREB) suppressed the VAMP2-EGFP punctum formation in axon terminals during synaptogenesis. Consistently, constitutively active PKA or CREB stimulated VAMP2-EGFP puncta formation. On the other hand, cyclosporine A treatment or suppression of nuclear factor of activated T cells (NFAT) activation prevented the axon terminal remodeling from complex to simple shapes during synaptogenesis. Consistently, expression of constitutively active calcineurin accelerated the axon terminal remodeling. These results suggest that calcineurin-NFAT signaling regulates axon terminal remodeling and PKA-CREB signaling controls synaptic vesicle accumulation.

As upstream signals of presynaptic differentiation, we focused on Ca²⁺ signaling since Ca²⁺/calmodulin is required for the activation of both calcineurin and some adenylyl cyclases. We showed that application

of Ca^{2+} /calmodulin inhibitor or olfactory sensory neuron-specific expression of calmodulin inhibitory peptide suppressed both synaptic vesicle accumulation and axon terminal remodeling. Thus, the trigger of presynaptic differentiation could be Ca^{2+} release from intracellular stores or Ca^{2+} influx. Application of a phospholipase C inhibitor or olfactory sensory neuron-specific expression of inositol 1,4,5-trisphosphate (IP_3) 5-phosphatase suppressed synaptic vesicle accumulation, but not morphological remodeling. In contrast, application of a voltage-gated Ca^{2+} channel blocker or expression of Kir2.1 inward rectifying potassium channel prevented the morphological remodeling. We also provided evidence that IP_3 signaling acted upstream of PKA signaling. Our results suggest that IP_3 -mediated Ca^{2+} /calmodulin signaling stimulates synaptic vesicle accumulation and subsequent neuronal activity-dependent Ca^{2+} /calmodulin signaling induces the morphological remodeling of axon terminals.

Mental retardation (MR), defined as a failure to develop cognitive abilities, is the most frequent cause of serious handicap in children and young adults. Nonsyndromic MR is characterized by reduced cognitive function without any other clinical features, thus providing the most direct approach to specifically study the neurobiology of cognition and pathogenesis of MR. The expression of Il1rapl 1b, the zebrafish orthologue of mammalian IL1RAPL1 responsible for a nonsyndromic form of X-linked MR, stimulated synaptic vesicle accumulation in the axon terminal of olfactory sensory neurons. On the other hand, the expression of Il1rapl 1b-P455H prevented the morphological remodeling of axon terminal from complex shape to simple ones. These results suggest that Il1rapl 1b regulates synaptic vesicle accumulation and morphological remodeling through the carboxyl-terminal domain and TIR domain, respectively. We thus provide evidence that mental retardation protein Il1rapl 1b plays an important role in the axon terminal differentiation during neuronal network formation. An intriguing possibility is that IL1 receptor accessory protein-like 1 may mediate upstream signals to induce axon terminal differentiation during synapse formation.

Synapse formation is the key step in the development of neuronal networks. Precise synaptic

connections between nerve cells in the brain provide the basis of perception, learning, memory, and cognition. Thus, elucidation of molecular mechanisms that regulate the formation and modulation of central synapses will be essential for the understanding of neural wiring, brain functions and mental disorders such as schizophrenia, autism and mental retardation.

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Pathology, Immunology and Microbiology

1. Pathology

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Introduction and Organization

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

Dr. Ota moved to Department of Pathology, Chiba University Hospital, as an Associate Professor on September, and Dr. Goto to Department of Pathology, Institute of Medical Science on December,

2010. Dr. Shibahara was promoted to a Lecturer on December, and Dr. Shintani was adopted to be an Associate on March, 2011.

In the new fiscal year, 2011, three new students will enter the postgraduate course, and there will be 15 postgraduates (including two foreign students).

We are responsible for the pathology practice of the University Hospital, and carrying forward the morphology-based research targeting human diseases. As for the education of Pathology, we take charge of the following courses for the medical students; General Pathology course for the 1st grade students in collaboration with Department of Molecular Pathology,

Systemic Pathology for the 2nd grade, Clinical Clerkship for the 3rd grade, and Bedside-learning (BSL) for the 4th grade students, respectively. Programs for postgraduates and junior residents are also included in our education activities.

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 (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, including thorax, liver, pancreato-biliary tract, urology, gynecology, breast, and orthopedics, as well as biopsy cases of liver, kidney and skin are discussed.

Clinico-pathological conferences (CPCs) for two autopsy cases are held every month in the hospital. Together with weekly autopsy conferences, they are useful for the education of clinical residents.

A model project for the survey analysis of deaths related to medical treatment (DRMT) has been in operation since September 2005. We have participated in the autopsy inspection of the project in corporation with Department of Legal Medicine. We have finished the two-year research project, “Feasibility of post mortem imaging as a method assisting the autopsy inspection of DRMT” (Grants-in-Aid from Ministry of Health, Labor and Welfare). The report is now open to the public and available at the website of the study group (<http://humanp.umin.jp/>).

Teaching activities

We take on General Pathology Course for the 1st grade of undergraduate students, especially in its morphological field. The course program and lecture notes are open to the public and available in UT Open Course Ware (<http://ocw.u-tokyo.ac.jp/>).

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).

Clinical clerkship for the 3rd grade, and BSL for the 4th grade are carried out. In BSL, 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. The past examinations for graduation and Systemic Pathology for the second grade students are referred to the website.

We also have charge of the lecture series of tumor pathology for the Cancer Profession Training Program in postgraduate school.

Research activities

The first major theme is “chronic inflammation and neoplasms”, especially Epstein-Barr virus (EBV) associated gastric carcinoma (GC) (Drs. Uozaki, Hino, Sakatani, Morikawa and Nakaya). We are focusing on mechanisms of abnormalities in CpG island methylation and microRNA molecules in the development and progression of EBV-associated GC (Shinozaki A et al. ref.34)

The second major theme is ‘traslational research pathology’. We are engaged in search of target molecules for cancer therapy by global analysis of expression profiles of various cancers, in collaboration with Research Center for Advanced Science and Technology (RCAST), the University of Tokyo. In addition, we take part in a global COE program, “Comprehensive Center of Education and research for Chemical Biology of the Diseases”, in which we are investigating the morphological analysis of gene expression abnormalities of the key molecules for several diseases (Dr. Yamauchi), aiming the development of new morphological methods and future application to diagnosis and therapy.

Dr. Ishikawa developed a new method for analyzing the precise copy number of genes in genome-wide scale (EG-method) in corporation with Prof. Aburatani (RCAST). EG-method enables high-precision measurement of gene expressions in each allele of individual person in genome-wide level. His group is applying the method to pathology research.

The third theme is to re-evaluate the disease

entities and tumor entities from the standpoint of classical histopathology. We clarified the entity of fetal type of gastric carcinoma (Ushiku T et al., ref.39), and the importance of fallopian tube epithelia for the development of ovarian cancers of serous subtype (Maeda D, et al., ref.17).

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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 working as the professor of the Department of Molecular Pathology from August 2000. Now, the Department consists of a professor, an associate professor, two lecturers, two assistant professors, one project assistant professor, technical assistants, and some research fellows, including 15 graduate students, 2 master course students, and 3 post-doctoral fellows.

Teaching activities

Our department takes responsibility for lectures on “General Pathology” for the undergraduate students of the Faculty of Medicine in collaboration with the staff of 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, since most of the experiments can be done at this floor. We have “Progress Meeting” twice a month and “Monday Seminar” once a month.

We have been doing collaboration with the Ludwig Institute for Cancer Research, Uppsala, Sweden for more than 10 years, and our collaboration between Sweden, the Netherlands, and Japan is supported by the Core-to-Core Program “Cooperative International Framework in TGF-beta Family Signaling” of Japan Society for the Promotion of Science (JSPS) (<http://c2ctgfb.umin.jp/>). We have annual TGF- β meeting in Sweden or in the Netherlands every autumn, and some graduate students participate in the meeting and orally present their results.

We are currently supported by the Global Center of Excellence (GCOE) Program for "Integrative Life Science Based on the Study of Biosignaling

Mechanisms" (from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan. This program stimulates interaction with students and scientists in the program as well as those from other laboratories (<http://www.coe.s.u-tokyo.ac.jp/integr-life/index.html>).

Graduate students also present data at various meetings, including Annual Meetings of the Japanese Cancer Association, and Annual Meeting of the Molecular Biology Society of Japan. At the corridor of our laboratory, posters of our graduate students reported at these meetings are presented.

Research activities

Our major research interest is to elucidate how members of the TGF (transforming growth factor)-beta family transduce signals, and how they regulate growth, differentiation, and apoptosis of various cells. We are also interested in the regulation of angiogenesis and lymphangiogenesis using embryonic stem (ES) cell-derived vascular progenitor cells and other endothelial cells.

Smads can be classified into three subclasses. Inhibitory Smads (I-Smads), i.e. Smad6 and Smad7 in mammals, are negative regulators of TGF-beta family signaling. I-Smads inhibit TGF-beta family signaling through multiple mechanisms, among which physical interaction of I-Smads with type I receptors and competition with receptor-regulated Smads (R-Smads) is the principal mechanism of their action. Smad7 inhibits all TGF-beta family signaling, while Smad6 inhibits BMP signaling mediated by BMP type I receptors ALK-3 and ALK-6. We reported that Smad7 has two modes of interaction with type I receptors. One is through the three-finger-like structure and the L3 loop in the C-terminal MH2 domain, while the other is through the basic groove in the MH2 domain. In contrast, Smad6 mainly uses the basic groove in the MH2 domain for interaction with type I receptors. Our findings revealed that Smad7 has an additional mode of interaction with type I receptors which is not shared with Smad6, and suggest that the mode of interaction with type I receptors may play unique roles in mediating the inhibitory effects of Smad7 (Kamiya et al. *J. Biol. Chem.* 2010).

Diffuse-type gastric carcinoma is characterized by

rapid progression and poor prognosis. High expression of TGF-beta and thick stromal fibrosis are observed in diffuse-type gastric carcinoma. We had previously shown that disruption of TGF-beta signaling by a dominant negative form of TGF-beta type II receptor (dnTbRII) in diffuse-type gastric cancer cell lines caused enhanced tumor growth through induction of tumor angiogenesis *in vivo*. We had also reported that repression of the expression of thrombospondin-1 (TSP1), a potent angiogenic inhibitor, is involved in the tumor angiogenesis regulated by TGF-beta signaling in diffuse-type gastric carcinoma. We now show that TGF-beta induces tissue inhibitor of metalloproteinase 2 (TIMP2) expression in the OCUM-2MLN cell line, and that expression of TIMP2 is decreased by dnTbRII. Enhanced tumor growth of the OCUM-2MLN cells by dnTbRII *in vivo* was abolished by overexpression of TIMP2. Interestingly, the degree of hypoxia in tumor tissues was increased and pericytes covering tumor vasculatures were decreased by TIMP2 in OCUM-2MLN cells. These findings suggest that the function of tumor vasculatures was repressed by TIMP2. Thus, the possible mechanisms of the increased angiogenesis in diffuse-type gastric carcinoma by dnTbRII is the down-regulation of TSP1 and that of TIMP2 (Johansson et al. *Cancer Sci*, 2010).

Arkadia is a positive regulator of TGF-beta signaling that induces ubiquitin-dependent degradation of some inhibitory molecules of TGF-beta signaling, including Smad7, c-Ski, and SnoN. We have found that Arkadia induces degradation of some other proteins and regulates signaling pathways other than TGF-beta signaling pathway. By yeast-two-hybrid screening for Arkadia-binding proteins, we found that the mu2 subunit of clathrin-adaptor 2 (AP2) complex interacts with Arkadia. The C-terminal YXXΦ-binding domain of the mu2 subunit interacted with the N-terminal YALL motif of Arkadia. We have shown that by interaction with the AP2 complex, Arkadia regulates EGF signaling by modulating the endocytosis of EGF receptor through interaction with AP2 complex (Mizutani et al., *J. Biochem.* 2010).

Epithelial-mesenchymal transition (EMT) is a crucial event in wound healing, tissue repair, and cancer progression in adult tissues, and TGF-beta is well known to induce EMT in normal and transformed

epithelial cells. We demonstrated that during the EMT process, TGF-beta induced isoform switching of various proteins, including fibroblast growth factor (FGF) receptors, causing the cells to become sensitive to FGF-2 (basic FGF). TGF-beta induced the expression of alpha-smooth muscle actin (alpha-SMA) in NMuMG epithelial cells. When FGF-2 was added together with TGF-beta, the cells no more expressed alpha-SMA, and showed a phenotype of activated fibroblasts through the MEK-Erk pathway activated by FGF-2. Consequently, normal epithelial cells that have undergone EMT by TGF-beta and FGF-2 promoted the invasion of breast cancer cells in vitro. These findings suggest that TGF-beta and FGF-2 cooperate with each other and regulate EMT in cancer microenvironment during cancer progression (Shirakihara et al. EMBO J., 2011).

We have organized the 59th Fujihara International Seminar "TGF-beta signaling and cancer" on July 14-17, 2010 in Tomakomai, Japan (<http://fis59.umin.jp/>; supported by the Fujihara Foundation of Science and the Core-to-Core Program of JSPS). More than 80 scientists and students participated in the Seminar, and exchanged their most recent data.

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Pathology, Immunology and Microbiology

2. Microbiology

Department of Microbiology

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Introduction and Organization

Professor emeritus Akio Nomoto who had been the chief of the Department retired in 2008 and moved to Microbial Chemistry Research Foundation as the Chairman of Board. From 2009, new Department of Microbiology started with Professor Masanori Hatakeyama as the new chief. The present Department consists of 20 members; 1 professor (Dr. Hatakeyama), 2 associates (Drs. Kamiya and Tsutsumi), 1 Post-doc (Dr. Seidi), 5 technical staffs (Ms. Yano, Morohashi, Yoshihashi, Goto, Azami), 11 Graduate School students (Ms. and Mrs. Takahashi, Fujii, Saito, Yamahashi, Hayashi, Safari, Suzuki, Kashiba, Yanagiya, Kikuchi, Nagase).

Teaching activities

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

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

Research activities

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.

1. Delivery mechanism of *H. pylori* CagA into gastric epithelial cells.

The lipid bilayer of the cell membrane is composed of the outer and inner leaflets, which comprise different phospholipid species. The outer leaflet is primarily made of phosphatidylcholine, whereas the

inner leaflet is characterized by the specific enrichment of amino phospholipids such as phosphatidylserine (PS), phosphatidyl ethanolamine (PE), and phosphatidylinositol (PI). We found that PS is rapidly and transiently turned over from the inner leaflet to the outer leaflet of the plasma membrane upon direct attachment of *H. pylori*. Although PS externalization is known to be an early sign of apoptosis, cells infected with *H. pylori* do not induce apoptosis. The transient PS externalization requires a live *H. pylori* and is induced by both *cagA*-positive and *cagA*-negative strains. Masking of surface externalized PS by Annexin V or anti-PS antibodies significantly inhibits delivery of CagA into gastric epithelial cells. The result indicates that the membrane exposed PS is involved in the translocation of *H. pylori* CagA.

Electron microscopic analysis revealed that CagA, which is secreted via the type IV secretion system, is fixed on top of the type IV syringe. The bacterial surface-exposed CagA protein then directly binds to PS that has been externalized on the host membrane. The CagA-PS interaction requires Arg-X-Arg (RxR) motif that is present at the middle portion of CagA. In order to examine if the CagA-PS interaction is critical for CagA delivery into host cells, we generated an *H. pylori* strain that produces a CagA mutant in which the PS-binding RxR motif was destroyed. Infection of gastric epithelial cells with *H. pylori* revealed that, in contrast to the wild-type CagA, the mutant CagA is not delivered into the host cells. The observation indicated that the CagA-PS interaction plays a critical role in the delivery of *H. pylori* CagA into host gastric epithelial cells.

An important question as to the translocation of CagA from the bacterial side to the host cell cytoplasm is whether host cell machineries, especially those mediating endocytosis, are involved in this process or not. Depletion of ATP in the host cells abolishes CagA translocation, indicating active role of host machineries in CagA delivery. However, inhibition of clathrin, dynamin, CDC42 or ARF6 did not influence translocation of CagA from the bacterium to the host cell. Likewise, inhibition of macropinocytosis by amiloride fails to inhibit CagA delivery. Hence, delivery of CagA via the type IV secretion system involves ATP-dependent host cell machineries, but do

not utilize endocytic processes known to date.

Upon delivery into gastric epithelial cells, CagA is localized to the inner side of the plasma membrane. This membrane tethering is also mediated at least partly by the interaction of CagA with PS, which is specifically distributed to the inner leaflet.

2. *H. pylori* CagA-mediated loss of epithelial polarity in the development of gastric carcinoma.

A series of studies with CagA-transgenic mice revealed that CagA has an oncogenic potential *in vivo*. In contrast, when expressed in non-polarized epithelial cells cultured *in vitro*, CagA potently inhibits cell proliferation. The CagA-mediated inhibition of cell growth is due to accumulation of p21 cyclin-dependent kinase inhibitor in response to Erk MAP kinase signaling, which is aberrantly activated by CagA. Cells growth-arrested by CagA-induced p21 become flat and express cell-senescence markers, indicating that CagA-expressing cells undergo senescence program. It is well known that non-transformed cells cease proliferation after a certain rounds of cell division. This phenomenon is called “replicative senescence”. In contrast, when cells received non-physiological stresses, they emergently turn on the senescence program and thereby stop proliferation. The cellular response is called “premature senescence”. One of non-physiological stresses that induce premature cell senescence is the activation of oncogene such as *ras* or *myc*. Indeed, aberrant activation of oncogenes in non-transformed cells efficiently induces premature cell senescence, which is currently thought to act as a cell-autonomous tumor suppression system that prevents malignant transformation. Our results therefore indicate that the *H. pylori* oncoprotein CagA also induces premature senescence by triggering oncogenic stress.

In the stomach, *H. pylori* delivers CagA into polarized epithelial monolayer that consists gastric mucosa, but not non-polarized epithelial cells. Accordingly, we expressed CagA in polarized epithelial cells and found that, under polarized condition, CagA expression induces abnormal cell proliferation through Erk activation without p21 accumulation. The finding indicates that CagA-deregulated Erk signaling can induce an opposite response in cell proliferation, premature

senescence or aberrant proliferation, in a polarity-context dependent manner.

Upon inhibition of RhoA small GTPase activity in polarized epithelial cells, CagA expression causes accumulation of p21 as is the case of non-polarized cells. Hence, the status of RhoA activation plays a key role in determining cellular response, either growth-arrest or proliferation, in response to CagA. RhoA activity is positively regulated by GDP/GTP exchanger (GEF) and negatively regulated by GTPase activating protein (GAP). Among various RhoA GEFs, GEF-H1 is known for its altered subcellular distribution that is dependent on epithelial polarity status. In non-polarized epithelial cells, GEF-H1 is localized to the cytoplasm, where the GEF activity is inhibited through binding with microtubules. In polarized epithelial cells, however, GEF-H1 is translocated from the cytoplasm to the plasma membrane, where it is concentrated to the tight junctions. At the tight junction, GEF-H1 is associated with its inhibitor cingulin and thereby functionally inactivated. This in turn indicates that release of cingulin from the GEF-H1-cingulin complex activates RhoA GEF activity of GEF-H1. When CagA is delivered into polarized epithelial cells, the bacterial protein is localized to the plasma membrane, where it is associated with SHP2 and PAR1. Now, we found that CagA-associated PAR1 also interacts with the GEF-H1/cingulin complex in polarized epithelial cells. Formation of the CagA/PAR1/GEF-H1 heterotrimeric complex causes a release of cingulin from GEF-H1 and thereby activates RhoA GEF activity in polarized epithelial cells. As long as a substantial amount of CagA is continuously delivered into epithelial cells, the CagA/PAR1/GEF-H1 complex is kept at the plasma membrane, preventing cytoplasmic redistribution of GEF-H1 even after cells become non-polarized. In contrast to the polarized cells, expression of CagA in non-polarized epithelial cells fails to generate the CagA/PAR1/GEF-H1 complex because GEF-H1 is present in the cytoplasm, making it difficult for CagA to activate RhoA.

RhoA activated by CagA in polarized epithelial cells then stimulates Rho kinase (ROCK), which in turn potentiates transcriptional activity of c-Myc through phosphorylation. The ROCK-activated c-Myc specifically induces microRNAs, miR-17 and miR-20a,

which target p21 mRNA and thereby prevent p21 accumulation.

This work uncovered a here-to-fore unidentified signaling pathway (GEF-H1/RhoA/ROCK/-Myc/iRNA/21) coordinating cell polarity and cell cycle. The work also reveals that *H. pylori* CagA is a unique oncoprotein that specifically triggers aberrant mitogenesis by deregulating the GEF-H1/RhoA/ROCK/-Myc/miRNA/p21 signaling pathway upon delivery into polarized epithelial cells.

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Introduction and Organization

The Department of Infection Control and Prevention started at first as the Division of Hospital Infection Control Services on January 23, 1991. This division developed into the Division of Infection Control and Prevention on September 1, 1993 and the present department on June 4, 1994. Currently, our faculty consists of one professor, five guest lecturers, four 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.

Teaching activities

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

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

Research activities

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

- 1) Development of preemptive strategies for the control of healthcare-associated infection
- 2) Development of new methods in infection control and treatment of viral hepatitis
- 3) 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

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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's adopted its present name when the late Dr. Tomio Tada took his position in 1977 as professor and chair of the department. 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 his retirement in 1994, Taniguchi had tried to follow and improve the high standards of the department by providing a first-rate education to students as well as performing cutting-edge, internationally recognized research in the field of immunology.

In the late 1970s and early 1980s, Taniguchi's research was the first to identify and subsequently characterize two cytokine genes, interferon (IFN)- β and interleukin (IL)-2. These initial studies led to the experimental dissection of the cytokine systems in the context of the regulation of immunity and oncogenesis. One of our major contributions resulting from these efforts was the discovery and characterization of a new family of transcription factors, termed interferon regulatory factors (IRFs).

While the core of our current research is aimed at clarifying the functions of IRF family members in the context of immunity, the broad scope of our scientific interests encompasses a number of areas including those

pertaining to innate immune system activation, autoimmunity, oncogenesis, and others. In addition, a new area of research was initiated on intestinal immunity.

Teaching activities

All members of our department take our responsibilities to teach and train the next generation of scientists very seriously. Our department provides class work instruction through lectures on immunobiology, immunochemistry and molecular immunology to the undergraduate students of the faculty, 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 during which time students present the progress of their own research projects, discuss the future directions of their own and the research of others, and are exposed to the latest, cutting-edge research questions confronting the field of immunology. We also offer a special training course (called 'free quarter') of basic and advanced biological and immunological techniques to medical students. In addition to lectures and laboratory courses provided by our own staff members, special seminars on leading research activities are also given by internationally recognized scientists from all over the world, such as Jeffrey V. Ravetch (Professor of The

Rockefeller University) and Shimon Sakaguchi (Professor of Osaka University).

Research activities

Our research interests within the fields of cellular and molecular immunology involve the extensive analysis of the mechanisms that underlie the regulation of gene expression and signal transduction in host defense systems, with a focus on the molecular mechanisms of the host defense against viral and bacterial infections. Among these mechanisms, the interferon (IFN) system is one of the most important in the control of such infections. During the course of our studies, we have identified members of the interferon regulatory factor (IRF) family to play a number of critical roles in immunity. In total, our studies on IRFs have revealed a remarkable functional diversity and serve as key regulators in the control of innate immune responses. For example, we have shown that the transcription factor IRF-7 is essential for type I IFN production upon virus- and TLR-activated signaling pathways. Furthermore, IRF-5 was demonstrated by us to be critical for the induction of pro-inflammatory cytokines and chemokine genes, which are typically activated by TLRs in response to infections.

The exposure of DNA within the cytoplasm of a cell, which can occur during the course of viral and bacterial infections, evokes strong, TLR-independent immune responses. Recently, we have identified a protein that functions as a cytosolic DNA sensor in these responses. DNA-dependent activator of IRFs (DAI) upon recognition of cytosolic DNA associates with TBK1 kinase and IRF3 transcription factor to induce transcription of type I IFN genes. Recently, we have established DAI-deficient mice and plan to investigate the physiological role of DAI. Central to protective and pathological immunities is the activation of innate immune responses by nucleic acids, which is mediated by the transmembrane Toll-like receptors (TLRs) and cytosolic receptors. In mammals, the transmembrane pattern recognition receptors TLR3, TLR7 and TLR9 respectively recognize double-stranded RNA, single-stranded RNA and hypomethylated DNA; while the RIG-I-like receptors (RLRs), namely, RIG-I and MDA5 are

known as cytosolic RNA-sensing receptors. In addition, cytosolic DNA-sensing receptors which include DAI, RIG-I/MDA5 and AIM2 also trigger innate immune responses. For all except AIM2, the hallmark of the innate immune responses activated by these receptors is the induction of type I IFNs, proinflammatory cytokines and chemokines. Our recent study revealed a hierarchy in the nucleic acid-mediated activation of innate immune responses, wherein the selective activation of the nucleic acid-sensing receptors is contingent on the promiscuous sensing by high-mobility group box proteins (HMGBs).

From the above new finding, we reasoned that nonimmunogenic nucleotides with high-affinity HMGB binding may function as suppressing agents for HMGB-mediated diseases, particularly those initiated and/or exacerbated by nucleic acids. We characterized an array of HMGB-binding, nonimmunogenic oligodeoxynucleotides (ni-ODNs). Interestingly, we found that binding affinity is for the most part independent of nucleotide sequence, but is instead dependent on length and the secondary structure of the deoxyribose backbone. We further showed that these ni-ODNs can strongly suppress the activation of innate immune responses induced by both classes of nucleic acid-sensing receptors. We also provided evidence for the suppressive effect of an ni-ODN, termed ISM ODN, on the induction of adaptive immune responses and in mouse models of sepsis and autoimmunity. Thus, our study suggests the possible use of these ni-ODNs in therapeutic interventions.

We also conducted applied research projects, in which we discovered several unique compounds that interfere with innate immune receptor signaling. One of these compounds turned out to be quite unique in that it activated stress-induced MAK kinases, JNK and p38 while inhibiting the activation of NF- κ B transcription factor. We have promising results, indicating the usefulness of this compound for the treatment of inflammatory autoimmune diseases and cancers. We aim at improving the efficacy of this compound by modifying its structure for clinical purposes and, at the same time, try to elucidate its mechanism of action.

Finally, we have also been conducting a new

research project focusing on the intestinal immune system and their relationship with the intestinal microbiota. The intestinal mucosa has a unique and complicated immune system composed of a variety of adaptive immune cell populations. In particular, CD4⁺ T cells in the intestinal mucosa comprise significant numbers of interleukin (IL)-17-producing cells ('Th17 cells') and IL-10-producing regulatory T cells ('Treg cells'). These cells are particularly abundant at the intestine and are present even at the steady state. Employing gnotobiotic techniques, we have demonstrated that components of the intestinal commensal microbiota, particularly segmented filamentous bacteria (SFB), strongly induce small intestinal Th17 cells, whereas the accumulation of Foxp3⁺ Treg cells in the colon of mice is promoted by the presence of the spore-forming component of indigenous intestinal microbiota—particularly the genus *Clostridium* belonging to clusters XIVa and IV. By extending our results, we are currently trying to develop new therapeutic strategies by intervention of the microbiota for various diseases including Crohn's disease and ulcerative colitis.

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Radiology and Biomedical Engineering

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Introduction and Organization

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

Clinical activities

Clinical services on Diagnostic Radiology, Nuclear Medicine, and Radiation Oncology are provided in the centralized Clinical Radiology Service Department in cooperation with radiology technologists and nurses.

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

In the section of Nuclear Medicine, there are two SPECT rooms and three PET rooms. These nuclear imaging procedures are chiefly performed and reported by radiologists and cardiologists.

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

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

radionuclide (RN) therapy in the same floor. In addition, four beds are allotted to terminal care ward located in the 14th floor.

Teaching activities

Lectures are given to the fourth-, fifth- and sixth-year students to provide fundamental knowledge of diagnostic radiology, radiation oncology and nuclear medicine. Professor, associate professors and lecturers as well as specialists assigned as part time lecturers take part in the education. A series of lectures about fundamentals of radiology and related sciences are given to the fourth-year students. As bed-side-learning (BSL) curriculum, small groups of the fifth-year students are taking part in mini-lectures and practice to learn basics of diagnostic radiology for one week. For the sixth-year students, another week of small group training and mini-lectures are prepared to learn 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 aspect of radiotherapy and the other is reduction of injuries due to radiation exposure. With the purpose of achieving precise external irradiation, a new linear accelerator with C-arm and 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 (Dyconic therapy) 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 for body tumors, such as lung and liver tumors, has been investigated. A new technology to track mobile tumors, represented by lung tumors is under investigation in collaboration with accelerator makers. Novel approach to terminal care of patients with various cancers has been investigated and implemented as the palliative care team in cooperation with expert nurses. The relationship between terminal condition and cytokines, and newly developed scoring system of quality of life are being evaluated. The gustatory injury due to radiotherapy has been investigated through animal experiments in combination with the laboratory of biological function, Graduate School of Agricultural and Life Sciences, University of Tokyo, and through taste tests in clinical setting. Radiation injuries in many tissues in the critically accident in Tokai-mura were also investigated.

Nuclear Medicine group promote clinical research on images of function by the application of radioisotope-labeled tracer technology. 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] H₂O, CO₂, O₂, CO, [F-18] FDG, [C-11] methionine, [F-18]Dopa, [C-11]NMSP, NMPB and [C-11] raclopride. 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] NH₃, TI-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

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Introduction and Organization

The Department 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. Former professor of our laboratory is Prof. Shogo Ueno, who extensively did the research of bio-magnetic imaging and magnetoencephalography of brain functions. After his retirement in 2006, Dr. Yasuteru Urano took up the post, and the new laboratory was launched since January of 2010. Dr. Mako Kamiya joined in May 2010 as an assistant professor, and one postdoc and one technician has joined by the end of March 2011.

Teaching activities

As for under-graduate education, our department takes a part in medical engineering lectures for the 3rd year medical students. As for PhD course education, our department delivers the lecture of fluorescence imaging for both master and doctor course students. Our laboratory is also accepting Free Quarter students every year, and this year we had two 3rd year students for one month and two 2nd year students for two weeks, respectively. They were trained to synthesize chemical probes and observe live cells with fluorescent microscopes.

Research activities

1. Development of novel fluorescence probes

By the end of March 2011, various instruments for chemical syntheses, purification, and characterization were settled in our department, i.e., four chemical hoods, four evaporators, two instruments for the purification of compounds based on different chromatographical mechanisms, two HPLC systems, 400 MHz NMR, ESI-TOF mass, and so on. UV-Vis spectrometers and fluorometers were also settled in our laboratory. So now, molecular design, chemical syntheses, purification, characterization of novel probes can be done in our department.

By using above instruments, we are now conducting various projects of establishing novel bioimaging techniques based on the development of new fluorescence probes. So far, we have succeeded in establishing rational design strategies of fluorescence probes based on photoinduced electron transfer mechanism. Further in 2010, we newly succeeded to establish another versatile design strategy by utilizing the concept of intramolecular spirocyclization.

2. Live imaging of cellular functions and in vivo tumors by precisely designed fluorescence probes

Various instruments for live imaging of cells and animals were already settled in our laboratory, i.e., confocal fluorescence microscope equipped with a white-light laser, wide field fluorescence microscope, FACS, in vivo fluorescent imager, in vivo

bioluminescent imager, fluorescent endoscope, etc. Also, instruments for cell culture and DNA work were also settled in our laboratory.

By using these instruments, we are doing live imaging of cancer cells and model mice extensively, for elucidating characteristic features of live cancer cells. Based on the acquired data, we are developing novel fluorescence probes for detecting tiny tumor sites in vivo. In 2010, hydrolase activities in cancer and normal cells were extensively examined by utilizing novel probes, and we found that some glycosidase and peptidase activities are truly upregulated in cancer cells. Further, we also succeeded to detect tiny tumor sites in cancer bearing model mice by applying appropriate fluorescence probes. Now, we start to apply these probes to real human resected tumor samples, and examine the efficiency of our probes.

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Introduction and Organization

Institute of Medical Electronics was established in 1963 as the first research institute for medical engineering in Japan. Department of Clinical Medicine in the Institute of Medical Electronics was started in 1964 for research and development of the advanced diagnostic and therapeutic medical engineering technologies for clinical medicine. 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 the Faculty of Medicine, Institute of Medical Electronics has been shifted to the Graduate School of Medicine, and the name of the department has been changed as shown above since April 1, 1997.

The current members include 1 associate professor, 1 lecturer, 6 graduate students, 1 professor emeritus, 2 research fellows, 17 visiting researchers, 1 technical staff, and 1 secretary.

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. Our doctor course students have the opportunity to perform research works under the guidance of Prof. Mabuchi at Department of Information Physics and Computing, Graduate School of Information Science and Technology.

Teaching activities

We take a part in systematic lectures for the 3rd year medical students, and provide practice in the “free quarter” course for the 3rd and 4th year medical students. In systematic lectures, we teach basic knowledge of the advanced diagnostic and therapeutic medical engineering technologies. The lectures of introduction 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. In the lectures for the master course students, we teach artificial organ technologies. In the lectures for the doctor course students, we teach philosophy, methodology and basic and special knowledge of advanced medical engineering technologies for basic and clinical medicine.

The educational practice of the post-graduate students is performed mainly by on-the-job training method in the daily research works. Pre-operative management, anesthesia, surgery, post-operative management, measurement, data processing, ethical factor, and other important information are acquired through the development and the animal experiment of the artificial hearts. 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 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 department.

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. Almost all the researches and developments for driving mechanisms, energy converters, blood pumps, artificial valves, biomaterials, power transmissions, measurement techniques, control methods, anatomical compatibility, hemocompatibility, tissue compatibility, computer fluid dynamics, 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 an implantable TAH. We invented a small continuous-flow blood pump with high performance, named undulation pump, for the implantable TAH. We are developing an undulation pump total artificial heart (UPTAH) using undulation pumps. The UPTAH is the most compact implantable TAH with the highest performance in producing output in the world. This TAH is designed to generate a pulsatile flow by changing motor speed periodically. Recently, the new model of a UPTAH was developed for the purpose of studying physiology with a nonpulsatile TAH. This UPTAH can switch a pulsatile flow to a nonpulsatile flow with a single device easily. We succeeded to survive a goat for 153 days with the UPTAH.

How to control the output of a TAH is another big interest. We have developed our original control method, named 1/R control. The 1/R control is a physiological flow control method of TAH developed with a conductance (1/R: reciprocal of a resistance) parallel circuit model. At the present time, the 1/R control is the only reported method to achieve physiological control of a TAH. 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 was changed in accordance with a metabolic demand of the animal.

The 1/R control was installed in the UPTAH and the pathophysiological study was performed with a nonpulsatile TAH. The result showed that the 1/R control could be possible not only with a pulsatile TAH, but also with a nonpulsatile TAH. The general conditions and organ functions were not changed by the application of the nonpulsatile mode. The cardiac output and the arterial pressure changed with the condition of the goat in the pulsatile mode and also in the nonpulsatile modes, which seemed almost identical. However, the sucking effect of atria was more significant in the nonpulsatile mode than the pulsatile mode. 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.

A new blood pump, named the helical flow pump (HFP), for the TAH is under the development. The HFP is a novel blood pump having a hydrodynamic levitating impeller. We are expecting to develop an ideal TAH that surpass the outcome of the heart transplantation with the technologies of the UPTAH, HFP, 1/R control, and hybrid materials described later. A project of the emergency life support system (ELSS) that is a compact and transportable percutaneous cardiopulmonary support (PCPS) device for emergency use has been started in 2004. The device consists of a blood pump, an oxygenator, a drive and control unit, and a battery unit. A new membrane oxygenator and a new blood pump were designed and integrated into one piece. An experimental model exhibited good performance. The improved model of the ELSS is under the

development to realize one-month support. 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 20 kg.

Concerning the biomaterials, we have been developing a new method to develop hybrid materials. In general, it is not easy to develop mechanical parts of implantable artificial organs from the components of living tissue because these components have insufficient strength and durability. To overcome these problems, an insert molding method, which is commonly used for the molding of resin 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 possibility. This year, with this insert molding technique, we started to develop the tip of the inflow conduit for the ventricular assist device. The tip of 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 tip was inserted was implanted under the skin of a goat. The experiments are going on. This hybrid technique will be important technology for developing the next generation artificial organs.

Concerning the measuring technique, an implantable video camera for observation of angiogenesis has been developed using a CMOS chip. This device is an evolved version of our implantable video camera for observation of microcirculation using a CCD image sensor. In the new devices, a scaffold was attached to the camera and was implanted in the animal. The camera having a polyglycolic acid fabric sheet as a scaffold was implanted in goats and succeeded to observe the real-time growth of tissue and micro blood vessels in the scaffold. The influence of cell seeding in the scaffold was studied. The subcutaneous tissue of a goat was cultured to obtain the seeding cells. These cells were seeded in the scaffold attached to the camera. The camera was implanted under the skin of the same goat. Another camera without cell seeding was also implanted in the same goat as a control study. The results showed that the growth speed of tissue and micro blood vessels in the scaffold

was faster in the cell-seeding scaffold than non-seeding one. The technique of the observation of microcirculation and angiogenesis will give important information for the studies of tissue engineering and regenerative medicine as well as the implantable artificial organs.

Our research of the IT (information technology) medicine is focused to the home medical care. The research and development of the IT infrastructures for monitoring the condition of the patients living at home is being performed. The miniaturized wireless ECG (electro cardiogram) 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 mobile computer receive the real-time data through the Internet lines from the data server. This system has been tested experimentally in a clinic and the operating records revealed that the system was very useful for the remote real-time monitoring of the patients at home. The system is being improved for general use in Japan.

Nerve interface will be very important technology for developing control mechanism of artificial organs. The basic study to develop a multiple interface array for brain machine interface is being studied at Prof. Mabuchi's laboratory, Department of Information Physics and Computing, Graduate School of Information Science and Technology.

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

serves as the PI of Japanese ADNI.

1. Research on β -amyloid and presenilins

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

of the γ -secretase complex harboring PS as the catalytic center, associated with three additional membrane proteins. They demonstrated that APH-1 and Nicastrin serve as the “stabilizing” co-factor of PS, whereas PEN-2 is the component that confers proteolytic activity to this complex. They also showed that PS, APH-1, nicastrin and PEN-2 are the essential set of proteins that comprise the γ -secretase complex (Takasugi et al. *Nature*, 2003). This study is highlighted as a milestone work that elucidated the mechanistic roles of protein cofactors in the formation and function of γ -secretase (see reviews; Iwatsubo *Mol Psychiatr*, 2004; *Curr Opin Neurobiol*, 2004). His group has also shown by establishing in vitro γ -secretase assays that sulindac sulfide, a major non-steroidal anti-inflammatory drugs, directly acts on γ -secretase and selectively reduce A β 42-generating activities (Takahashi et al., *J Biol Chem*, 2003), providing important implications to the therapeutic strategies of AD by γ -secretase modulation. Recently, he has established a novel method for an efficient in vitro reconstitution of γ -secretase complex, paving the way towards the structural analysis of active γ -secretase (Hayashi et al. *J Biol Chem*, 2004), and using thus highly purified γ -secretase particles, they have partially unveiled the submolecular structure of this complex by single-particle EM analysis (Ogura et al. *BBRC*, 2006). Very recently, his group has established an elegant strategy to analyze the structure-function relationship within the catalytic structure of γ -secretase complex by cystein chemistry, and demonstrated that γ -secretase harbors a water-permeable catalytic pore (Sato et al. *J Neurosci*, 2006), and that substrate proteins enter the catalytic pore through the lateral gate located at the C terminal side of PS (Sato et al. *J Neurosci*, 2008). Thus, Dr. Iwatsubo’s group started from an elegant immunohistochemical analysis of A β deposits in AD brains and extended it to a contemporary molecular/cellular biology of PS, that proved to play a key role in the important biological reaction termed “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 they have characterized a wide spectrum of α -synuclein pathologies in neurodegenerative disorders.

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

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

a unique membrane-spanning structure. CLAC has been highlighted as a protein that may affect fibrillization of A β and contribute to amyloid plaque formation. Indeed, he has recently shown that CLAC-positive senile plaques constitute a unique subset of plaques distinct from the classical, β -sheet-rich amyloid deposits, underscoring the pathobiological role of CLAC in amyloid formation (Kowa et al. *Am J Pathol*, 2004), and that CLAC inhibits fibrillization of A β in vitro (Osada et al. *J Biol Chem*, 2005). Transgenic mice studies are confirming the role of CLAC in the morphogenesis of senile plaques in vivo.

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 35 clinical sites nationwide, and preparing all the infrastructures required for the large-scale clinical study. The J-ADNI group is starting to recruit participants on June 2008 (total, 600 cases for 5 years), and the instruments and framework of J-ADNI are being adopted in multiple global clinical trials in Japan.

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Introduction and Organization

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

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

What are the precise nature and the whole

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

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

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

Following the retirement of Professor Tatsuya Haga (who became the President of Life Sciences Institute at the Faculty of Science at Gakushuin University) in March 2001, and the departure of Associate Professor David Saffen to initially University of Minnesota and then to Ohio State University in August 2001, Associate Professor Haruhiko Bito was appointed as Head of Department since January 2003. The Department is located on the 6th floor, in the West wing of the third building of the Medical School. The Department currently enrolls one associate professor, three assistant professors, two

postdoctoral scholars, one technical staff member, four Ph.D. and three M.S.-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 under the auspices of the Global Center of Excellence Program Grant "Global Center of Education and Research for Chemical Biology of the Diseases". This 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).

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. Currently, experiments are ongoing to capitalize on this knowledge in order 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.

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, Ageta-Ishihara et al., *J. Biol. Chem.*, 2003; Takemoto-Kimura et al. *Neuron* 2007). This novel membrane-bound CaMK (CLICK-III/CaMKI γ) is most expressed in the central nucleus of the amygdala and in the ventral medial hypothalamus, while also being present at a much weaker amount in most central neurons. Ongoing biochemical and cell biological studies indicate a critical role for lipidification of this kinase to be properly sorted into specific lipid-restricted membrane microdomains. The function played by this lipidified, membrane-inserted CaMK in circuitry formation and maturation was scrutinized using RNA interference. Along with the identification of the critical lipid-modifying enzyme that controls lipid-anchoring of this kinase, we discovered a novel activity-regulated mechanism whereby CLICK-III/CaMKI γ is actively sorted into dendritic lipid rafts, where it specifically regulates Rac-mediated actin remodeling that is required for BDNF-stimulated dendritogenesis (Takemoto-Kimura et al., *Neuron*, 2007; Takemoto-Kimura et al. *Eur. J. Neurosci.* 2010). Similar studies in axonal growth also suggest the active contribution of CaMKK cascade in this process (Ageta-Ishihara et al., *J. Neurosci.* 2009; Takemoto-Kimura et al. *Eur. J. Neurosci.* 2010).

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

these newly synthesized gene products affect synaptic protein complexes (Okuno and Bito, *AfCS/Nature Mol. Pages*, 2006).

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

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

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

PNAS, 2002).

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

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

Whether similar or distinct mechanisms also operate during spinogenesis and spine maturation remains to be determined, though a role for Rho and

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

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

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

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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 weekly journal club to present papers closely related to member's research field. Moreover, 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 generating fluorescent probes for live cell imaging

Imaging techniques which visualize signaling molecules in living cells is a powerful method to understand the mechanism underlying physiological functions. To facilitate this process, we developed a high-throughput screening system based on 96-well plate format protocol. After screening, we obtained glutamate indicators consisting of many combinations of the cysteine mutant and the fluorescent dye showing large fluorescence changes upon glutamate binding. This result suggests 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 synapse physiology by glutamate imaging technique

In mammalian central nervous system, direct imaging of neurotransmission should greatly contribute to clarify exocytosis dynamics at synapses and improve our understanding of the mechanisms in synaptic transmission. Aiming at imaging glutamate, we developed a novel optical glutamate probe by our high-throughput screening system. We successfully visualized 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) Study of regulation mechanism of cell movement by fluorescent imaging of Rho family proteins

We have constructed new fluorescent indicators for Rho family, including Rho, Rac and Cdc42, which

function as molecular switches in many signaling cascades. These indicators revealed spatial-temporal dynamics of Rho family proteins activation in randomly migrating HT1080 cells. In contrast to previous studies, Rho and Cdc42 were activated in broad areas of the plasma membrane in motile cells. Therefore, our probes can be used for more effective and quantitative study for cell movement. Furthermore, in a central nervous system, Rho family is known as a molecules regulation cell motility of neuronal cells and synaptic function. We applied our fluorescent probes to experiments for analysis of these cell functions.

4) Novel technology for construction of genome-wide RNAi library

RNA interference (RNAi) using short hairpin RNA-expressing vectors (shRNA vectors) is a powerful maneuver for functional genomics. We have previously reported a method called EPRIL (enzymatic production of RNAi library) by which shRNA vectors are produced from a cDNA fragment through multiple enzyme reactions. Recently, we have tried to improve the original EPRIL method to enable constructing a genome-wide RNAi library. The improved EPRIL method was successfully adapted to 96-well plate format which allows high-throughput production of shRNA vectors. Using EPRIL technology and imaging techniques, we explore physiologically functional molecules by a high-throughput screening system.

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Neuroscience

2. Integrative Medical Neuroscience

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Introduction and Organization

Speech and language are the most prominent cognitive functions distinguishing human being from non-human animals. The Department of Cognitive Neuroscience aims at basic, interdisciplinary studies on human cognitive functions ranging from perception, action, attention, memory, language and thought. Many studies are conducted in cooperation with other departments, faculties and universities such as in the field of engineering, physiology, psychology, education and clinical neuroscience.

Teaching activities

1. Graduate Course
 - Introduction to Neuroscience
 - Imaging Neuroscience
2. Undergraduate Course
 - Introduction to Medical Biology

Research activities

We all know that our perception, action, emotion, thought and consciousness depend on the activity of neurons in the brain. But we know very little about how the neurons do these jobs. The aim of cognitive neuroscience is to clarify the neural mechanisms of our mental activity. Conventional and still very powerful approach is to devise a task paradigm that

represents the psychological phenomenon in question and measure the brain activity while the experimental subjects perform the task. Studies to date have identified neural correlates for varieties of mental activities.

Here in this lab, we attempt to go beyond the simple correlation between brain activity and behavior. The key questions are the following. .

- Behavioral significance: You've got nice activation in some parts of the brain. Is the activity truly associated with the behavior? Is it necessary for the behavior? In other words we are interested in the causality of the brain activity to behavior.
- Temporal dynamics: The temporal order of the events in the brain is not enough to understand the neural mechanisms. Let's clarify the causal relationships between the activations in different brain regions.
- System dynamics: Do not be satisfied with pretty brain images with blobs. Neurons are useless unless they transmit impulses to other neurons. It is the bi-directional interactions between multiple brain areas that make us perceive, feel, and think. I am now interested in the dynamics in the transition between symmetric and asymmetric impulse transmission between brain areas.
- Information-based analysis: We can tell what a person is thinking about based solely on his brain activity. Do not be surprised. Everyone in this field knows that. But what does this tell us about the brain?

This decoding technique can be used to demonstrate that the brain is the cause of our cognition.

To answer these questions we are using various behavioral paradigms such as selective attention, task switching, perceptual decision making, masked priming and so on. We are interested in the mechanistic explanation of brain function. Students and younger researchers are free to choose any kind of behavioral paradigms if we agree that the paradigm is the best one to answer the questions about the brain.

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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. Three professors are administrating Department of Child Psychiatry, the University Hospital also, and trying to utilize its clinical activities for research more effectively.

Teaching activities

As the year of 2010 was the first year of this department, we had no graduate students. However,

we were involved to supervision of research projects about autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) by three graduate students from Department of Neuropsychiatry.

Research activities

Main subjects of our research are ASD including autism and Asperger syndrome, 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 2010 are as follows:

- Behavior phenotype, neuropsychological and genetic 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

Neuroscience

3. Clinical Neuroscience

preschoolers and group cognitive behavior therapy for adults with high-functioning ASD

(Details can be found in the report of Department of Child Psychiatry.)

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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 begun to focus on basic and clinical neuroscience in pervasive developmental disorders (PDDs). From 2006, we have been working in the new closed ward (30 beds) and in the open ward (29 beds). 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 outpatient services, we have more than 20 staff

psychiatrists, 4 clinical psychologists and 1 psychiatric social worker. Approximately 1100 new patients visited yearly (2010), and the total visits per day was about 160.

The secluded ward has 29 beds including 3 seclusion rooms. We also have 31 beds for the open general ward. Approximately 550 patients with various psychiatric disorders were admitted in a year (2010). Recently, the number of patients who were referred from the emergency unit is increasing. The age of patients is variable from teenager to senior. The majority of the patients are schizophrenia, mood disorder and psychosis based on the somatic disease. Mean hospitalization is 30 day long, and modified electro-convulsive therapy was performed for over 400 patients.

We established 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.

From the last year, new diagnostic program using near infrared spectroscopy (NIRS) has started as an advanced medical treatment.

Teaching activities

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 (2nd year), bedside learning (3rd year), and clinical clerkship (elective for 4th-year students). For postgraduate, currently more than 20 neuropsychiatry Ph.D. students are studying.

This year, Mental Health research course has started as one of 10 programs for the education in clinical research field.

Research activities

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

1) Neuroimaging

Our research plays a leading role in psychiatric neuroimaging in Japan and aims at multi-modality neuroimaging (structural and functional MRI, MR spectroscopy, EEG, MEG, near-infrared spectroscopy [NIRS], PET) in schizophrenia, mood disorders, pervasive developmental disorders, and posttraumatic stress disorder (PTSD).

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 been

focused on Epilepsy, PTSD, autism and schizophrenia.

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). A number of candidates of the susceptible genes are studied using case-control and TDT (transmission disequilibrium test) designs.

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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. We celebrated 40th Anniversary of the Department of Neurology in 2004.

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 headaches.

In the in patient ward, we offer programs for postgraduate education including the program for the first stage postgraduate education. We also offer the excellent training program with the goal to get the board of Neurologist. In 2005, we initiated deep brain stimulation for the treatment of movement disorders in cooperation with Department of Neurosurgery. Clinical trials including that for polyglutamine disease and that based on vestibular nerve stimulation are being conducted.

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 bed-side learning for the 5th grade medical students, and clinical clerkship for the 5th grade medical students.

In the bed-side learning we include small group lectures covering neurological examination, neurophysiology, neuroradiology, neuropathology, neuropsychology, neuroimmunology, and neurogenetics. 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.

For training of board-certified Neurologists, we offer the excellent program including patients' care, training in Neurophysiology and Neuropathology, consultation for Neurology, and supervising of junior trainees. This program is integrated with clinical practice at the affiliated hospitals where rich experience is obtained for numerous cases in Clinical Neurology.

In Graduate School, we offer highly advanced research activities based on the interest of graduate students. In 2003, 21st Century COE program started in the Neuroscience Division, and we have successfully completed the program. Following the 21st Century COE program, we started "Global Center of Education and Research for Chemical Biology of the Diseases" as a Global COE program, in 2008.

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 a high throughput DNA-microarray-based diagnostic system. This system provides comprehensive analyses of genes including those for Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, and familial spastic paraplegia. We have discovered that glucocerebrosidase gene (GBA) confers a strong risk with an odds ratio of 28.0 for susceptibility to Parkinson disease. This finding was further confirmed by international collaboration. A high throughput pipeline for linkage analysis was established, which was applied for linkage analysis of many neurodegenerative diseases. Large-scale genome

analysis employing next generation sequencers were initiated to identify causative genes for familial neurologic diseases. We have initiated multicenter-based consortium for multiple system atrophy. A large-scale genome-wide analyses are being conducted to identify disease susceptibility genes. We have established excellent animal models for dentatorubral-pallidoluysian atrophy, and conducting studies for development of therapeutics. As the new protein degradation pathway, the role of autophagy was investigated. (Tsuji, S., Goto, J., Shimizu, J., Takahashi, Y., Ichikawa, Y., Momose, Y., Date, H., Iwata, A., Fukuda, Y., Jin, Y., Suzuki, K., Nakahara, Y., Seki, N., Mitsui, J., Ishiura, H., Ihara, R., Hahimoto, A)

Development of pathomechanism-based therapy for amyotrophic lateral sclerosis (ALS) is a mission of neurologists. In motor neurons of sporadic ALS patients, naturally occurring RNA editing of glutamate receptor subunit GluR2 is inefficient in a neuronal class-selective and disease-specific manner. Because RNA editing at the GluR2 Q/R site is specifically catalyzed by ADAR2, we developed mice in which the ADAR2 gene was conditionally targeted. By analyzing these mice, we demonstrate that failure to edit the GluR2 Q/R site is the primary cause of death of motor neurons. Based on these findings, we are currently involved in the development of specific therapy for ALS. (Kwak, S., Hideyama, T., Yamashita, T., Teramoto, S., Hachiga K., Kaneko, S., Chai, H.)

The human neurophysiology section has been studying normal function of the human brain and pathophysiology for neurological disorders using several non-invasive physiological methods, such as TMS, EEG, MEG, fMRI, NIRS and EOG. Our final goal is to develop a new therapeutic method for intractable disorders. One of them is deep brain stimulation (DBS) which has been partly established. We began a physiological approach to elucidate the therapeutic mechanisms for DBS in the patients. We have also recently developed a new, highly effective TMS method to induce long-term effects on the human brain using repetitive, monophasic magnetic stimuli. We have just started a project to treat patients with movement disorders, intractable pain, epilepsy and so on using that new treatment. (Terao, Y., Hanajima, R., Okabe, S., Matsumoto, H., Furubayashi,

T., Higashihara, M., Shiota, Y, Ohminami, S., Tsutumi, R.)

In the field of neuromuscular diseases, we provide pathological diagnosis of biopsied materials from patients with myopathy or neuropathy. We also provide autoantibody testing for anti-ganglioside antibodies, muscle specific antibodies and paraneoplastic neurological antibodies. In research field, using biopsied muscles and collected serum samples, we have been studying the mechanisms of inflammatory myopathies especially in polymyositis, cancer associated myositis, dermatomyositis, collagen disease associated myositis and myositis with autoantibodies. We have also been studying the mechanism of muscle fiber regeneration in various myopathies including inclusion body myositis. We aim to increase understanding of the etiology and pathogenesis of neuromuscular diseases. (Shimizu, J., Hashimoto, H., Kubota, A., Tokimura, N., Sagishima, M., Tokimura, N., Nishizawa, M.).

Department of Molecular Neuroscience on Neurodegeneration is funded by Janssen Pharmaceuticals. Several projects are ongoing/ We found new ubiquitin ligase UHRF-2 and new ubiquitin-like modulator FAT10 related to the pathogenesis of polyglutamine diseases. Studies on epigenetics of Parkinson's disease revealed abnormal epigenetic changes in the disease. We also reported a novel mutation of aceruloplasminemia (Iwata, A., Hyashi, H.).

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Introduction and Organization

The Department of Neurosurgery at the University of Tokyo Hospital consists of 13 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 seven 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. The incumbent professor, Dr. Nobuhito Saito, has been serving as the fourth professor since 2006.

Our department provides expertise for patients with brain tumor, cerebro-vascular disease, spinal lesion, functional disorders, head trauma, etc.

three days a week (Monday, Wednesday and Friday). New patient are accepted two days a week (Tuesday and Thursday). Specialized outpatient clinics are open for patient with brain tumors, pituitary disease, spinal disease, cerebrovascular disease, endovascular intervention, epilepsy, and gamma knife treatment. From April 2010 to March 2011, 15,572 patients were treated at the outpatient clinics.

The Neurosurgery Ward has about 40 beds on the seventh floor of the new hospital building opened in Sept. 2001. In 2009 and 2010, 771 and 874 patients were admitted to the Neurosurgical Ward, respectively. Three hundred and ninety one and 426 surgical procedures were performed with 134 and 150 gamma knife precedures in each year. Our practice covers a wide variety of neurosurgical diseases including malignant and benign brain tumors, hemorrhagic and occlusive cerebrovascular diseases, spinal disorders, epilepsy, pain and movement disorders.

Clinical activities

General and specialized outpatient clinics are open

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 27 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 9100cases.

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 6 residents in 2010 as a neurosurgical residency program. These residents are trained in the university hospital and affiliated hospitals to experience every aspects of neurosurgical practice for five years in average. Our residency training is finalized after the sixth year, when the finishing residents serve as senior resident at the university hospital for 6 months. Academic training is provided through numerous intramural clinical and research conference, journal clubs seminars as well as quarterly regional meeting of Japan Neurosurgical Society. After the residents finish their training, or during training, they can choose to be admitted into the Ph.D. course at the graduate school of Medicine, University of Tokyo, to be involved in advanced basic research activities for 4 year. After complete training, our graduates stay in the department to be an associate in our or other university hospitals or become clinical staff in our affiliated hospitals.

Research activities

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

Our department has been keeping 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

Despite advances in microsurgical techniques, the poor prognoses of malignant glioma patients have not improved for decades. We develop a new strategy by using replication-competent herpes simplex viruses (HSV) that are genetically engineered to replicate in and kill tumor cells but not normal cells. Using a third-generation oncolytic HSV, we are currently conducting a clinical trial on patients with progressive glioblastoma. We are also conducting clinical research for immunotherapy with human umbilical vein endothelial cell (HUVEC) as a vaccine. To develop novel strategy for the treatment of malignant gliomas, we have isolated brain tumor initiating cells (BTICs), which are supposed to be responsible for resistance to conventional therapy, from surgical specimens, and we are studying specific targeting therapy against BTICs.

We also practice optimized therapy based on the

results of genetic analyses routinely performed on tumor specimens obtained from glioma patients.

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 are now establishing 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 electrodes.

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) 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.

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

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

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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 and fourth 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 thirty members in our department, including research fellows, graduate and undergraduate 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 and fourth 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. Takebe), Kanazawa University (Dr. Matsugo), Kyoto University (Dr. Koizumi), Environmental Science Center of The University of Tokyo (Dr. Karima), 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) Establishment of pathophysiological roles of chemokines in vivo in various animal disease models.
- 2) Molecular analysis of chemokine receptor signaling pathway.
- 3) Genome-wide transcriptome and epigenetic signature of various types of cells and tissues in normal as well as disease state
- 4) Development of vaccines against pathogenic microorganisms and cancer
- 5) Establishment of a novel bio-monitoring system for environmental chemicals.

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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 Private (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 the Faculty of Medicine, the University of Tokyo. In 1995, the Department became a part of the 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 the 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.

Currently, the Department consists of four faculty members above listed, three supporting staffs, 11 graduate students (nine in PhD program and two in MPH program), one research students, 15 part-time lecturers, and 12 visiting fellows.

Teaching activities

1) Undergraduate Program (Medical School)

In the winter term of the fourth grade in the School

of Medicine (M2), students are provided with the following lectures; current issues of public health, preventive services, epidemiology, health economics, community health and medicine, occupational and environmental health, infection and tuberculosis control, mental health, human ecology, international health, current health policy and administration in Japan, quality of care, and so on. Similarly, in the sixth grade (M4), a concentration course of public health (e.g., health care systems, occupational medicine, and community health practice) 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 spring 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 Faculty of Arts and Sciences, the School of Integrated Health Sciences, and the Faculty of Engineering in the University of Tokyo.

2) MPH Program

The Department offers two lectures and one field practice; “Health Policy,” “Public Health Preparedness,” and “Public Health Practice.” The Department also provides a research course for individual students.

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

We are interested in the topics of health care system and economics in general. We have performed and published those studies related to delivery of health services in Japan; such as supply and distribution of physicians, the separation of pharmaceutical dispensing and prescribing in medical practice, cost studies of outpatient and inpatient services, and the efficiency and equity issues of the Japan's health insurance system. We have also carried on health services research, such as quality of care. These studies have been published in international policy 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 Thailand, 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) Collaboration with overseas institutions

We have done a couple of studies in collaboration with overseas institutions, such as the study of factors associated with diagnosis delays of tuberculosis in the eastern region of Afghanistan, and the study of preventive behaviors among people living with HIV in Khon Kane, Thailand.

4) Academic meeting

We held the Fifth Annual Conference of Japan Health Economics Association at Tetsumon Memorial Hall and seminar rooms, Graduate School of Medicine,

the University of Tokyo, on July 10, 2010.

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Social Medicine

2. Forensic Medicine, and Medical Informatics and Economics

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Introduction and Organization

Associate Professor Kuniyoshi Katayama lectured “judicial medicine” in University of Tokyo since 1882 before our department was founded as the first department of forensic medicine in Japan in 1888. He renamed “judicial medicine” to “forensic medicine” in 1891 since the department should cover legislation as well as general forensic practices. Dr. Katayama became the first professor of forensic medicine in Japan.

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

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

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

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

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

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

The present Professor Ken-ichi Yoshida has studied the mechanism of ischemic heart disease and sudden cardiac death related to emotional stress, with respect to gap junction, intracellular signaling, and proteolysis.

The department currently has one professor, one lecturer, two assistant professor, one associate, two special technicians, nine postgraduate students, and one researcher. Three doctors from this department have become professors since 1999. It is a nationwide difficulty to find suitable doctors as forensic pathologists. However, there are not a few doctors who want to become the graduate students in our department. Those who have experience in clinical practices, and researchers in biochemistry, physiology, pathology, and molecular biology are welcome. We are preparing to teach practice and research for the future forensic pathologists.

Forensic autopsy

The determination of precise cause of death is the most important mission of our department. We autopsy about 120 criminal cases in eastern part of Tokyo every year. We have already autopsied more

than 11,000 cases since 1897. Some of these cases are very famous in criminology in Japan.

In forensic autopsy, we examine the pathological, alcohol, toxicological, and blood type testing of each case, too. Finally, forensic pathologists in our department diagnose the cause of death. Expert opinions express the cause of death and forensic judgment for each case. We have kept them since first autopsy case in 1897. We have serious responsibility in the determination of cause of death.

Since 2005, we also performed autopsies on medical practice-related deaths (MPAD) in corroboration with Department of Human Pathology. The both departments lead the pilot study on the investigation and analysis of MPAD (supported by government). We also contribute to evolve new way of presenting expert opinions for the jury courts that has been enacted in 2009.

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 are based on the autopsy and court cases for the better understanding of the death investigation and medical law. In the Free Quarter training course, students experience laboratory practices (toxicology, DNA typing, histology) or experiments. In the clinical clerkship, each student experiences the process from autopsy to presentation of expert opinion. They can also attend the practices of medical examiner's activities and the court.

In addition, students of school of public health and (undergraduate & graduate) law school are provided with somewhat practical lectures with exercises.

Research

Our mission is to determine the cause of death in unnatural deaths through autopsy and various examinations. We have also tried to find problems in legal-social systems related to death investigation, court procedure, and patient safety. To improve death investigation and related legal-social systems, we

conducted variety of researches including cardiovascular basic sciences, legal-social medicine, forensic pathology, toxicology, and DNA polymorphism as described below.

1. Molecular mechanism of myocardial lesions and cell death in ischemia-reperfusion

We autopsy many cases suddenly died in association with accidents, violence, restraint, or medical practices. Particularly, cardiac lesion and arrhythmias related to a brief ischemia and emotional stress respectively are important in forensic practices. The diagnosis and demonstration of scientific evidence are very difficult in these cases. Contraction bands, often found in sudden cardiac cases, are reproduced during reperfusion following brief ischemia. We have found that contraction bands propagate through Gap Junction (GJ), and derangement of sarcoplasmic (SR) calcium handling. Additionally, we found that calpain (calcium-dependent protease) contributes to the myocardial injury, contractile dysfunction and development of infarction in reperfusion. We study the mechanism of these phenomena in the models of coronary occlusion, isolated perfused heart, or cultured cardiomyocytes through circulatory physiology, biochemistry, histology, and molecular biology. The results will warrant a better understanding of the aforementioned diseases, and potentially useful diagnostic methods for sudden death cases.

2. Research on arrhythmic death related to emotional stress, diseases, or drugs.

GJ functions are disturbed in myocardial infarction and heart failure. Restraint of these persons often causes sudden death. With pharmacological GJ inhibition, restraint induces lethal ventricular tachycardia/fibrillation in rats. The restraint of the rat is well-known model to investigate cardiovascular response to emotional stress. We also study the mechanism of arrhythmogenesis in the model of heart diseases and amphetamine treated animals.

3. Research on cardiovascular risk and sudden death in sleep apnea syndrome (SAS)

This is the most challenging theme in the field of cardiovascular research, but the production of a good animal model has been difficult. We have

successfully developed an apparatus for the rat model of SAS, and have undertaken the investigation on the molecular mechanism of cardiac hypertrophy, hypertension, and arrhythmias. We have organized multi-facility research groups to promote the project, after the Ministry of Education, Culture and Sport has accepted our proposal as the class A grant.

4. *Lesion propagation in rat model of brain contusion.*

We study the mechanism underlying the propagation of neural death through the cortical layer VI through GJ, activation of calpain and astrocyte.

5. *Development of a kit for ethnic affiliation.*

We are developing a novel practical method for determination of the ethnic affiliation using single nucleotide polymorphisms (SNPs).

6. *Investigation on the law and social system related to death investigation, medical safety, and lawsuit.*

We found that the disclosure of the information and bereavement service related to medicolegal autopsy are limited. Additionally, the information related to medicolegal autopsy cannot be used for accident prevention. Moreover, ethical problems are to be addressed for the research or educational purpose.

The Department of Health, Welfare, Labor, and Sports has promoted the model project on the investigation of medical practice-associated deaths (MPADs), and been trying to establish the new investigative system for MPADs. We have contributed to the review of the model project, and submitted reports on review and recommendations.

With corroboration with the society of emergency medicine, we have conducted a questionnaire study on the usefulness of feedback of autopsy information to the frontline of medical practices.

7. *Development of new methods for forensic examinations*

Through the experience in forensic practices, we have adopted or developed new methodology for toxicological analyses. Additionally, we developed new methods for forensic practices such as the production of distribution map of planktons in different river and sea areas.

8. *Case studies and forensic pathology.*

We have reported rare cases related to clinical medicine or potentially therapeutic deaths, for the

training or education of graduate students or young pathologists. Recently, we reported three cases as the first autopsy case or new disease modality.

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Department of Medical Informatics and Economics

Professor

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Introduction and Organization

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

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

The professor of the department also holds the position of director of the department planning, information and management (DPIM) in the University of Tokyo Hospital. DPIM is the department that deals with information analyses and future planning for the University of Tokyo Hospital by using information systems as well as the planning, design, development, and operation of information systems for the whole hospital. The DPIM was newly

established on April 1, 2003, after integration of the Hospital Computer Center and the project team for hospital development, which separately existed until the end of March, 2003.

Since the professor runs the Department of Medical Informatics and Economics with staffs of DPIM, they are practically the same organization. Therefore, educations and researches in the graduate course are promoted together with DPIM activities. Only one professor is the dedicated faculty member of the Department of Medical Informatics and Economics, however, faculty outside the department participates as teaching staffs of the graduate course: Assoc. prof. S. Koike and Lecturer. K. Miyo from DPIM, Assoc. Prof. H. Yasunaga from the Department of Health Management and Policy, Assoc. Prof. H. Fujita from the Department of Ubiquitous Health Informatics, Assoc. Prof. R. Yamamoto from Interfaculty Initiative in Information Studies, Graduate School of Interdisciplinary Information Studies.

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, and he is now an emeritus professor of the University of Tokyo. 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. One post for associate professor was transferred from the Department of Medical Informatics and economics to the Interfaculty Initiative in Information Studies and then our department started the wide acceptance of students. Assoc. prof. Y. Onogi assumed the start-up position, and now Assoc. prof. R. Yamamoto takes over the position.

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

Teaching activities

1). 4-year Ph.D. Course in the Department of Medical Informatics and Economics at the Division of Social Medicine: The Department of Medical Informatics and Economics at the Division of Social Medicine offers the Medical Sciences doctoral course (4-year program) and admission is open to those who graduate from a 6-year program at the Faculty of Medicine (the School of Medicine), and those who complete the master course either in the University of Tokyo or any other institutions (not necessary to be a doctor). Students will acquire Doctoral Degree (Ph.D.) of Medical Science with completion of required units and passing a doctoral thesis.

2). 3-year Ph.D. Course and 2-year M.H.S course in the Department of Health Informatics at the Division of Health Sciences and Nursing: The Department of Medical Informatics and Economics is a collaborating department with the Division of Health Sciences and Nursing at the Graduate School of Medicine, and it is called the Department of Health Medical Informatics. At the Department of Health Medical Informatics within the Division of Health Sciences and Nursing, the department offers the Master course in Health Science and Nursing (2-year program) and the Health Sciences and Nursing doctoral course (3-year program). In the master course, students will acquire Master of Health Sciences with completion of required units and passing a master's thesis. In the

doctoral course, students will acquire Doctor of Health Sciences(Ph.D.) with completion of required units and passing a doctoral thesis.

3). 2-year M.P.H and 1-year M.P.H in the Department of Health Informatics in the School of Public Health: We offer 2-year Master of Public Health (M.P.H) course and the 1-year M.P.H program in the School of Public Health. See the homepage of the School of Public Health.

4). 2-year M.M.S in the Department of Health Medical Informatics in the Medical Science Graduate Program: Graduate School of Medicine, the University of Tokyo, offers the master course in Medical Sciences. The course was established for students who graduate from faculties other than a 6-year program at Faculty of Medicine and eventually wish to advance to the Medical Sciences doctoral course of the University of Tokyo. It enables students to enroll in the department they plan to carry out their research for Doctor of Medical Science. (the entrance examination required for enrollment in Medical Sciences doctoral course) In this Master's course, all students entering the course spend the first four months taking formal coursework for students of all divisions, and then will decide which department they wish to affiliate with. At the department students are expected to conduct their research for the Master and complete a master's thesis in the last one and an half year. They will acquire the Master's degree (in Medical Sciences) with completion of required units and passing a master's thesis. Our department also accepts students in this course.

The enrolled students in FY2010 are one in doctor's course for Medical Informatics and Economics, one in master's course for Health Informatics.

The students' researches cover various topics; development of self medication management system using smart-phone devices, medical ontology, 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) studies on medical safety information systems, 3) medical knowledge discovery and analysis

of medical economics indicators by using databases of hospital information system and electronic health records system, 4) structured representations and standardization of medical terms and concepts, 5) , 6) privacy protection and security in healthcare information systems, 6) information analysis on food safety, 7) analysis of various issues on DPC.

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

- 1) A study on development methods for large scale ontology databases of medical terms and concepts :
This research develops the methods to build the large scale medical ontology, which is a database for hundreds of thousand of clinical terms and concepts and their relationships. It focuses on the development of basic methods for making and accessing databases and will be applied for the research.
- 2) Development of standardized IT infrastructure for clinical researches (Funding Program for World-Leading Innovative R&D on Science and Technology: the FIRST program, 2010.3-2014.3)
This research develops autonomic, distributed, real-time clinical support system. This project is a part of the FIRST program; "Development of Medical Technology for Treating Intractable Cancers and Cardiovascular Diseases" supervised by Professor Ryoza Nagai in the Department of Cardiovascular Medicine.
- 3) A study on Natural Language Processing of Clinical Document (Industry-academia collaboration project with Fuji Xerox Limited, 2007-2011). This research is on extracting medical knowledge such as time-oriented clinical events and adverse drug reaction of patients from electronic medical records.

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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 is actively involved in clinical medicine, basic research and teaching. In line with the rapidly evolving and progressing nature of modern treatment of cardiovascular diseases, our department has changed dynamically during the recent years. Not only do we have the most highly advanced equipment and facilities (e.g. 24-hour cardiac care unit), but are personnel are also highly trained to be well knowledgeable and expert in the most modern methods of diagnosis and treatment. As a teaching and research hospital, we also emphasize the development and incorporation of new treatments if they may benefit the patient. From a research standpoint, our interests range throughout all fields of cardiovascular medicine ranging from molecular biology to clinical research including genomics. Importantly, our research interests are aimed at making possible new diagnostics and treatment of cardiovascular diseases. Finally, we have a particular interest in teaching not only for medical students but also for residents which is important for the future of cardiovascular medicine.

Outline of department

Staff: one professor (Ryozo Nagai), 1 associate professor (Yasunobu Hirata), 2 assistant professors (hospital ward Hiroshi Yamashita and outpatient clinic Koichiro Kinugawa), 15 research associates, 5 staff members, 38 graduate school students, and 2 members studying abroad.

Clinical activities

In 2010, 1,611 patients were newly admitted to our hospital ward of approximately 50 beds. Of these patients, approximately 70% were due to ischemic heart disease. Cardiovascular angiograms were conducted in 2,144 patients, of which 635 cases were interventional procedures. CT coronary angiography was examined in 360 patients and cardiovascular MRI in 67. For arrhythmias, there were 94 cases of implantation of a pacemaker, 73 cases of catheter ablation, and other specialized pacemaker devices such as 12 cases of implantation of a cardioverter-defibrillator, and 14 cases of implantation of a cardiac resynchronization device.

As we are an authorized facility for heart

transplantation, left ventricular assist device (LVAD) use for severe heart failure cases has been increasing. In 2006, the first case of heart failure from our department underwent a heart transplant procedure at the Department of Cardiovascular Surgery. The hearts were transplanted to 6 cases also in 2010 (total 15 cases). Duration of hospitalization is on average 12.6 days.

Out-patient clinics are available as part of the Department of Medicine or as a specialized department. The profile of diseases includes ischemic heart disease in main and heart failure and arrhythmia in addition to hypertension and peripheral artery disease. Out-patient clinics are open both mornings and afternoons from Monday to Friday. Approximately 220 patients visit each day. Acute cases of coronary heart disease and aortic disease are also a focus of the department, as emergent catheterization is available on a 24-hours basis.

Teaching activities

As a division of the Department of Medicine, medical diagnostics training, general cardiovascular medicine, clinical lectures and bedside teaching are courses available at the medical school. For bedside teaching, two students are placed under the guidance of one research associate allowing for teaching in small groups. Specialized groups provide lectures. As for post-graduate education, residents are educated through specialized group conferences, grand rounds and clinical conferences.

Research activities

Areas of interest are as follows:

1. Interplay between organs, cells, and molecules in chronic inflammation
2. Cardiac hypertrophy and heart failure: analyses of pathogenic mechanisms and development of novel therapies (gene therapy, etc.)
3. Transcriptional regulation of various genes involved in cardiovascular development and pathogenesis
4. Differentiation of smooth muscle cells (atherosclerosis and restenosis after vascular interventions)
5. Nitric oxide and endothelial function
6. Mechanisms for cardiorenal association
7. Regeneration therapy for cardiovascular disease
8. Genetic polymorphisms and risk factors in cardiovascular disease
9. Optimization of individual treatment using the Computer Heart Simulator
10. Development of new integrated databases for clinical information and research
11. Investigation of disease pathophysiology and development of novel therapies (severe heart failure, cardiac transplantation, congenital heart disease)
12. Anti-arrhythmia therapy using catheter ablation
13. Diagnosis and treatment of Marfan syndrome
14. New treatment for pulmonary hypertension
15. Ischemic heart disease in patients with diabetic retinopathy
16. Aerobic threshold and cardiac rehabilitation
17. Imaging techniques (echocardiography, MRI, CT, RI) in cardiovascular diseases

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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 50 members belong to the Department. In the University of Tokyo Hospital, about 20 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 the 21st century. In this era, we are conducting basic and clinical researches for wide variety of respiratory disorders including 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 tools to manage these pulmonary diseases.

Clinical Activities

The Department of Respiratory Medicine is responsible for the out-patient care as well as care of in-patients (40 cases on average), which is taken at the 13th 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 bronchogenic carcinoma, respiratory infections, interstitial pneumonia, COPD and asthma. There are many emergency visits and admission due to pneumonia, respiratory failure, 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. 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 is appreciated as prototype of Cancer Board of the University of Tokyo Hospital, which launched four

years ago, and is now 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 from other departments.

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. Respiratory infections are now the 4th leading cause of all death and COPD will be the 5th leading cause of all death in the near future. In 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 2010

1. Primary lung cancer	497
2. Respiratory infection	86
3. Interstitial pneumonia	47
4. COPD	26
5. Asthma	14

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 Tuesday 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, bedside learning for the 5th year medical students, and clinical lectures for the 5th and 6th year medical students. Clinical clerkship for the 5th year students is actively performed in collaboration with expert doctors 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 lung cancer and pneumothorax, and try to discuss with the students several important points for planning 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 bedside learning, the students have 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 bedside learning and this lecture is highly appreciated by the students.

Clinical clerkship at the 5th year of the educational program is actively performed to facilitate the early exposure to the clinical practice both at Tokyo University 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 such as medical treatment of lung cancer are also provided. Each student is expected to learn and acquire the professionalism required for a medical doctor during this period.

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, chest imaging, pneumonia, COPD and so on are held at regular interval.

Research Activities

Our department is conducting basic and clinical researches for many respiratory disorders including lung cancer, COPD, asthma, interstitial pneumonia, respiratory infections and others. Epidemiological, clinical, cellular and molecular biological techniques are utilized for the elucidation of pathogenetic mechanisms and for the development of novel diagnostic and therapeutic modalities in respiratory medicine. Postgraduate students as well as the Faculty members make considerable studies about genetic alterations in lung cancer in collaboration with the Faculty of the Department of Thoracic Surgery, cell biological analysis using airway epithelial cells, fibroblast and smooth muscle cells, 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.

Molecular analysis of ion channels expressed on airway smooth muscle cells and lung cancer cells.

Exploration of diseases-susceptibility genes in respiratory diseases.

Analysis of disease-models using genetically engineered mice.

Analysis of DNA methylation and miRNA in lung cancer and its clinical application.

Elucidation of molecular mechanisms of diseases using conditional vectors for siRNA knockdowns.

Analysis of functional alterations of airway epithelial cells and fibroblasts in relation to tissue repair and remodeling in asthma and COPD.

Studies on pathogenesis of tobacco-smoke induced respiratory diseases using mouse model of long-term tobacco exposure.

Search for predictive factors for responses to chemotherapy in malignancy including lung cancer.

Takahide Nagase is GOLD National Leader; APSR, Chair of Central Congress Committee; and Program Officer, Research Center for Science Systems, JSPS.

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Introduction and Organization

The Department of Gastroenterology was established through a re-organization of the Graduate School of Medicine and that of the Division of Internal Medicine of The University of Tokyo Hospital in 1998. The department is responsible for clinical services, education and research activities in the field of liver, pancreato-biliary and digestive canal. It is comprised of a professor, 3 lecturers, 20 associates, 15 fellows, 62 graduates and 5 other visiting researchers including students from abroad (March, 2011). 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, forth, fifth and sixth 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 96 inpatients on average, which are about 2,800 in total per year. We receive about 110 new patients in and out of the hospital each week, with an average hospital stay of 12.3 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 (1063 cases in 2010). Number of treatments for hepatocellular carcinoma treatments, represented by percutaneous radiofrequency ablation, exceeded 900 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 (129 cases in 2010). 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.

In the pancreato-biliary field, ERCP is performed for more than 900 cases each year. The number of patients treated for choledocholithiasis with endoscopic papillary balloon dilation method exceeds 1,000, which is possibly the largest in the world. Endoscopic metallic stenting is an effective palliative care for malignant obstructive jaundice (60 patients a year). Covered metallic stent placement has been performed in a total of 700 cases, which may be the world's largest number. Pancreatic interventions such as pancreatic stenting, cystic drainage, endoscopic stone extraction and lithotripsy using ESWL (extracorporeal shock-wave lithotripsy) are performed for many challenging cases. Also we have applied the EUS-guided techniques to various clinical treatments.

In the gastrointestinal field, ESD (endoscopic submucosal dissection) is performed as a curative endoscopic treatment for neoplasms in esophagus, stomach or colon (200 patients a year). Endoscopic variceal ligations for esophageal varices (80 patients a year) are also frequently done. As a big breakthrough in this field, double-balloon endoscopy and capsule endoscopy have been introduced recently, which enabled the examination of whole small intestines. All those interventions are performed by the members of the department, specially trained for each technique.

In addition, for the management strategy against inoperative malignancies, we effectively combine the interventional treatments with various chemotherapy regimens using new molecular-targeting drugs.

On outpatient basis, ultrasonography is performed on 15,000 patients, gastroduodenal endoscopy on 8,200, and colonoscopy on 3,800 patients each year, leading the detection of about 170 cases of gastric cancer and 210 cases of colorectal cancer annually. About 50 % of them are treated endoscopically, but we also aim to perform basic studies using specimen, and turn these efforts to clinical activities.

Educational Activities

Systematic and clinical lectures on gastroenterology are regularly given to undergraduate medical students by staff members of the department. In addition, several courses of practical teaching are provided for the students. In particular, the Department of Gastroenterology makes much of the importance of bedside learning for the fifth grade students, where each student is allotted to an inpatient by joining the group of physicians and offering the opportunity to learn digestive diseases practically. The results are reported to the professor at the end of the course in the style of oral examination. Students are also required to summarize and outline articles from world's leading medical journals.

Residents of internal medicine join the Department of Gastroenterology for 1-6 months in rotation in their first year as a doctor, where they learn therapeutics and diagnostics in gastroenterology together with general internal medicine. Giving presentations at the scientific meeting is highly encouraged. If they are interested in gastroenterology in particular, they may learn advanced techniques in gastroenterology in affiliated hospitals for a few years. Usually, they will come back to the department after that period, and improve their clinical skills still further while at the education course. The majority of them also become graduate student, and starts medical researches either in a basic or clinical research area. Currently, the department has 74 students who were graduated from more than 30 medical schools in Japan.

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, mechanisms of liver regeneration and fibrosis, pathogenesis of *Helicobacter pylori* infection, role of miRNA in hepatocarcinogenesis, etc.

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 clinical trials of molecular target drugs for advanced hepatocellular carcinoma, erythropoietin for anemia introduced by interferon with ribavirin therapy, TS-1 alone or combined with gemcitabine, for pancreatic and bile duct cancers, gemcitabine alone or combined with cisplatin, additional mosapride in therapy of gastro-esophageal reflux disease, and investigation and treatment trial of the small intestinal lesions in NSAID users by capsule endoscopy.

The department is dedicated to pursuing better medical services from all facets of the subspecialty of gastroenterology, which is brought about by both basic and clinical researches.

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Internal Medicine

2. Medicine II

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Introduction and Organization

The Division 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, and other 2 associates are involved mainly in the Hemodialysis Unit. We are intimately working together in all clinical activities

under the supervision of the Professor and the Associate Professors.

Clinical activities

The residents are in charge of up to 30 patients of our division and supervised by associates and faculty staffs. Every Tuesday, we have a clinical conference 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 almost once a month.

Nephritis should be morphologically diagnosed by renal biopsy and the optimal treatment should be chosen for each patient. In our division, 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 division also works at the hemodialysis unit, thus we can manage patients in every stage of renal disease.

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 divisions concerning disorders of water and mineral metabolism.

Education

We have responsibility for educating undergraduate, graduate students and residents. Our staffs take part in several lectures for undergraduate and graduate students. In addition, our members are actively involved in bed-side learning and clinical clerkship of undergraduate students, and other clinical practice. In the ward, we are also educating residents during daily clinical works and periodical lectures concerning kidney and endocrine diseases.

Research

In our department there are more than 30 students of the graduate school. We have research conferences

every Tuesday, 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 division and outside the University including foreign countries. Achievements of our researches are published in world top level journals of nephrology, hypertension and endocrinology.

Affiliated Endowed Chairs

Department of Clinical Renal Regeneration

Introduction and Organization

Department of Clinical Renal Regeneration was founded by a donation from MOCHIDA Pharmaceutical Co., Ltd. in November 2002 as one of the departments of Division of Tissue Engineering in The University of Tokyo Hospital. The main object of this department is to contribute to the development of better treatment and drug discovery through tissue engineering technologies and regenerative medicine.

Research activities

We aim at clinical application of kidney-derived adult stem cell, clinical application of new scaffold material and matrix for renal regeneration and clinical renal regeneration by using cord blood. To achieve these goals, we are conducting research on adult stem cell biology in regeneration, comprehensive research on stem cell dysfunction in renal failure and development of 3-D culture system for induction of metanephros in vitro.

Department of Clinical & Molecular Epidemiology

Homepage

http://www.h.u-tokyo.ac.jp/research/center22/contribute/rinsyo_bunshi.html

Introduction and Organization

The Department of Clinical & Molecular Epidemiology was established in June 2004 as an endowed department (Mitsubishi Tanabe Pharma Co., Ltd.) of the Graduate School of Medicine, the University of Tokyo. Our department also belongs to the 22nd Century Medical Research Center, which partly represents the translational research activities of The University of Tokyo Hospital. Our department is established with the main aim of performing the clinical and epidemiological analysis on the metabolic syndrome in the Japanese population, of isolating susceptibility gene(s) to metabolic syndrome through molecular and genetic analysis on human and rodent animal models, and of contributing to the development of novel diagnostic method and therapeutic agents for the prevention and treatment of the cardiovascular diseases.

Research activities

Our research field of interest covers the followings.

- Identification and isolation of novel susceptible genes and related factors to metabolic syndrome through systemic molecular and biological analysis on human and rodent animal models of metabolic syndrome.
- Performance of clinical and epidemiological analysis with regard to metabolic syndrome.
- Development of novel diagnostic method for risk factors of cardiovascular diseases.
- Contribution to the development of preventive and therapeutic novel agents to treat patients with metabolic syndrome.
- Exploration of novel mechanisms of action of available pharmaceutical agents to treat patients with cardiovascular diseases.

Department of Molecular Vascular Endocrinology

Homepage

<http://plaza.umin.ac.jp/~kid-endo/07-lab/17-issikilab/issikilabtop.html>

Introduction and Organization

Department of Molecular Vascular Endocrinology was founded in June 2009 as an endowed department (Novartis Pharmaceutical Co., Ltd.) of the Graduate School of Medicine, the University of Tokyo. The main object of this department is to investigate molecular mechanisms and pathophysiology of vascular dysfunction caused by risk factors such as hypertension or atherosclerosis. Final goal of our research is to contribute to the prevention and therapy of cardiovascular disease.

Research activities

Our current research interests are as follows:

- Imaging and discovery of a novel regulatory system of endothelial function in view of intracellular signaling molecules such as Ca^{2+} or cAMP.
- Investigation of novel and known substances such as H_2S that can affect vascular function and analysis of the mechanisms.
- Exploration of novel diagnostic markers and therapeutic tools for endothelial and cardiovascular dysfunction.

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 the metabolic diseases from 3 former departments of Internal Medicine were unified to the Department of Metabolic Diseases. The Department of Metabolic Diseases is one of the major divisions in the Department of Internal Medicine at the University of Tokyo, and covers metabolic diseases including diabetes mellitus, obesity and dyslipidemia.

Under the supervision and direction of the previous professors Dr. Satoshi Kimura (1998-2003) and Dr. Toshiro Fujita (2003) and currently Professor Dr. Takashi Kadowaki (2003-present), we have been providing a wide-ranged clinical, teaching and research activities. Currently, we hold 35 beds

mainly on the 12th floor of the North Wing Ward A and the 4th floor of the Ward B of the Tokyo University Hospital, and take care of more than 30 inpatients constantly. Besides the staffs listed above, our division holds faculties in branches, for example, Department of Integrated Molecular Science on Metabolic Diseases (Associate Professor, Dr. Toshimasa Yamauchi and Assistant Professor, Dr. Masato Iwabu), Department of Molecular Physiology on Energy Metabolism (Associate Professor, Dr. Naoya Yahagi and Assistant Professor, Dr. Hironori Waki), Department of Translational Systems Biology and Medicine Initiative (Associate Professor, Dr. Naoto Kubota and Assistant Professors, Drs. Iseki Takamoto and Ryo Suzuki), The Clinical Training Center (Lecturer, Dr. Kazuo Hara), Department of Patient Safety & Risk Management (Assistant Professor, Dr. Kenji Harada), Division of Biophysics, Center for Disease Biology and Integrative Medicine

(Lecturer, Dr. Noriko Takahashi), and Division for Health Service Promotion, The University of Tokyo (Assistant Professor, Dr. Takayoshi Sasako). 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 around 20 students of Graduate School in our division. With all these 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 more than 6500 patients. On the inpatient ward, we not only take care of more than 30 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 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 day in the inpatient ward, and also give lectures twice a week in the outpatient unit. In addition, in collaboration with ancillary staffs of our hospital, we provide patients well-reasoned instructions regarding nutritional management, exercise therapy and medical therapy.

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

Teaching activities

As for medical student education, our department

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

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

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

During the period of bed-side learning, 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. Lectures that lead to profound understandings of the metabolic diseases are regularly provided by the staff physicians.

In clinical clerkship, 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.

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 new treatment.

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, we are 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, using a number of transgenic and knockout animal models. 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. In addition, we have been successfully unraveling the molecular mechanisms of β cell proliferation. We believe that these findings will lead to novel therapeutic strategies for diabetes and the metabolic syndrome.

2) Analysis of a glucose transport mechanism in insulin resistance

We analyze insulin-stimulated and contraction-induced glucose transport with technique of molecular biology. In addition, we try condition of a patient elucidation of diabetes and establishment of a new treatment by analyzing a diabetes model animal and mechanism of insulin resistance in a cultured cell.

3) 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, fatty liver, diabetes, hyperlipidemia and atherosclerosis using strategies of molecular biology and genetic engineering techniques.

4) Lipid disorders and atherosclerosis

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.

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Introduction and Organization

Department of Hematology and Oncology is responsible for clinical activities in out-patient as well as in-patient clinics of hematological disorders, conducting research activities for hematology and oncology, and are also in charge of teaching activities for undergraduate medical students, graduate students. We are also engaged in post-graduate, continued education to develop many hematologists of eminent distinction. These activities are performed by the united efforts of all members who belong to the department. Mineo Kurokawa, M.D., Ph.D. was installed as Professor of Department of Hematology and Oncology in 2005. The staff of Department of Hematology and Oncology consists of about twenty members including one professor, 2 lecturers, one special lecturer (hospital), and 6 associates.

Clinical activities

On average, 60-70 patients with hematological diseases are treated in the ward. Clinical facilities

include patient rooms with high-efficiency particulate air filtration and filtrated water supply. Patients who are eligible for the treatment with high-grade infection prophylaxis are admitted to the facilities. Patient care is provided by team management and three doctors composed of each one of junior residents, senior residents, and associates are assigned to one patient. Since clinical issues especially for patients with hematological tumors are highly related to the hamatopoietic stem cell transplantation, all clinical conferences are shared with staff members of the three departments, Hematology and Oncology, Cell Therapy and Transplantation, and Pediatrics. A number of clinical problems involved in the patient management are discussed in the morning clinical conference held every other day. Diagnostic and therapeutic issues as well as pathological aspects of thought-provoking cases are also discussed twice per month in the clinical conferences, each focusing on hematological diseases, lymphomas, or hamatopoietic stem cell transplantation.

Approximately 40 patients with acute leukemia, 150 with malignant lymphoma, 40 with chronic

myelogenous leukemia, 20 with multiple myeloma, 80 with myelodysplastic syndrome are annually admitted to our ward. Out-patient clinical services are provided daily in the morning and afternoon using three booths. Approximately 1200 patients are monthly consulted by our out-patient clinic. One of our final goals in the clinical activities is to cure all patients with hematological malignancies.

We perform various kinds of genetic or molecular analyses to detect, characterize, and monitor malignant cells and make use of them for diagnosis and planning of treatments.

Here are some technical aspects on the treatment strategy:

1. High-dose chemotherapy with or without autologous stem cell support: Adequate high-dose chemotherapy is administered for the treatment of malignant disease. For the autologous stem cell support, peripheral blood stem cell is usually selected as a source of stem cells.
2. 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 in cooperation with Department of Transfusion Medicine. Recently, transplantation after pre-conditioning of reduced intensity (RIST for reduced-intensity stem cell transplantation) is commonly performed for the elderly patients and patients with organ damages. The development of this strategy is expanding the eligibility of transplant recipients. Allogeneic hematopoietic stem cell transplantations for the elderly are performed under the admission of ethical committee of the Faculty of Medicine. Cord blood cells are also used as the sources of hematopoietic stem cells.
3. We also started the clinical study of maintenance therapy after autologous stem cell transplantation of multiple myeloma patients under the admission of ethical committee of the Faculty of Medicine.

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

Courses for bedside learning 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 that are erudite both in general internal medicine and in hematology and oncology. During the one-week case-oriented course, students 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 performed. 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 tumors, (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. 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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The Department of Allergy and Rheumatology presently consists of 10 staff mentioned above, who preside over 6 medical staff, 9 graduate students for "Doctor of Medical Science" and 1 staff studying abroad. 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 Internal Medicine Research Ward.

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 covers 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 10 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) Analysis of regulatory T cells.
- 2) Analysis of the mechanisms of tolerance breakdown to systemic autoantigens using transgenic mice.
- 3) Analysis of antigen specific T cell clonalities in immunological disorders.
- 4) Genetic analysis of rheumatoid arthritis and other connective tissue diseases.
- 5) Development of new gene therapies for immunological diseases.
- 6) Analysis of the mechanisms of oral tolerance.
- 7) Analysis of signal transduction mechanisms in immunological disorders.
- 8) Development and analysis of animal models of bronchial asthma.
- 9) Study of signal transduction of IgE mediated mast cell activation.
- 10) Regulation of IgE antibody production.
- 11) Analysis of cytokines and chemokines in the pathogenesis of allergic conditions.
- 12) Analysis of interstitial pneumonitis associated with connective tissue diseases,
- 13) Mechanism of drug allergy

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Introduction and Organization

The Department of Infectious Diseases has been one of the leading academic organizations specialized for internal medicine, in particular, infectious disease medicine in Japan since 1998, when the Departments of Internal Medicine, established in 1890, were rearranged into new ones according to subspecialty of internal medicine. Our department has been chiefly engaged in clinical, educational and research activities for infectious diseases including bacterial, fungal and viral infections of all organs including HIV infection, tuberculosis and viral hepatitis. Our department is located on 11th floor of the University of Tokyo Hospital Building, and has well-furnished research laboratories including P-2 class laboratory, a departmental library and a computer room as own properties. In clinical and research activities, we are collaborating with the Department of Infection Control and Prevention. An associate professor, 6 guest lecturers, an associate, 2 graduate students 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 11th floor of the Ward A of University of Tokyo Hospital. Diseases include HIV infection, viral hepatitis, pneumonia, resistant bacteria infections such as MRSA, BLNAR or VRE, tuberculosis, EBV infection, CMV infection, parasite

infection, *etc.* Every effort is made to give patients the best care and best quality of life. Clinical associates, full-time staff and residents take care of inpatients. The case presentation by residents is held on a weekly basis. Weekly clinical conference is held for discussing about all cases, in particular, those with 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 such SARS or avian influenza virus, which appeared recently.

Teaching activities

Our department takes a part in clinical lectures and bed-side learning of the internal medicine for undergraduate medical students according to the educational programs of the University of Tokyo. For the fourth year medical students, six lectures of infectious diseases are given. In addition, principles of medical diagnosis are taught at the bedside. During the bed-side teaching for fifth and sixth year students, our associates teach them on man-to man basis the basic way of thinking for correct diagnosis and therapy, the techniques of interrogation and physical examination, the way for interpretations of laboratory tests and other medical examinations, and the basic medical

procedures on each case. The education of junior residents is performed as described in “Clinical Activities”.

Research activities

Both clinical and basic researches are necessary to improve the diagnosis and treatment. The members of our department are doing best to obtain new findings using highly sophisticated methodologies. A monthly 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, CMV infection and tuberculosis (*Mycobacterium* 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) Establishment of the criteria for prediction and early diagnosis of CMV infection associated with HIV infection.
- (6) Innovation of new methods to control viral hepatitis or prevent the development of hepatocellular carcinoma in chronic viral hepatitis.
- (7) Establishment of the effective infection control method of MRSA and other MDRO infection.

- (8) Elucidating the mechanism and signal transduction of bacterial infection through toll-like receptors.
- (9) Analysis of intracellular function and signaling of the proto-oncogene Cbl.
- (10) Establishment of new methods for practical diagnosis and treatment of respiratory infection.

Members

Hiroshi Yotsuyanagi, Takeya Tsutsumi, Shuji Hatakeyama, Shu Okugawa, Shintaro Yanagimoto, Yohko Nukui, Atsuhito Fukushima, Keita Tatsuno, Sohei Harada, Koji Goto, Mahoko Ikeda, Koh Okamoto, Yoshitaka Wakabayashi, Tetsuro Kobayashi, Haruka Nakamura, Makoto Saito, Hideki Hashimoto, Kohei Harada.

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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 professor, one associate professor, two associates, and 5 adjunct professors, and other members are 3 senior residents, 6 graduate students, and 3 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 2010 January to 2010 December, 58 patients 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 2010 January to 2010 December, the numbers of the new outpatients and of the overall outpatients in our department were 123 and 3131, respectively.

Teaching activities

We are giving 6 methodical lectures on psychosomatic medicine for fourth grade medical students, 'problem-based learning' lasting 12 weeks (net 24 hours) for 6 or 7 fourth grade students, 'bed-side learning' for fifth grade students lasting two weeks, 'clinical clerkship' for 3 to 4 fifth grade students lasting 4 weeks each, and clinical lectures on psychosomatic diseases in cardiology for fifth grade students and on eating disorders for sixth grade students. We are trying to teach them not only basic knowledge of specific diseases, ways of physical examination, or interpretation of laboratory data, but also relevant ways of clinical interview, doctor-patient relationship building, and behavior modification.

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

Research activities

Targeting stress-related diseases such as not only those covered by our department but also other lifestyle-related disease, and cancers, we are investigating their pathophysiology and psychopathology through assessing bio-psycho-behavioral time-series data, various questionnaire data, and autonomic nervous function. We are also actively conducting basic as well as clinical research on eating-related substances.

Some representative research methods are as follows:

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

Six graduate students and 7 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-transfusional complication, and the previous professor, 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, 1 nurse 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. 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 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, immunotherapy of cancer patients and patients with recurrent abortion, and collection and preservation of peripheral blood stem cells are also performed.

- 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, HAB, ATLA and HIV antibodies;
 - 4) HLA typing for bone marrow and organ transplantation;
- III. Clinical work
 - 1) Pre-operative autologous blood collection and preservation;
 - 2) Lymphocyte vaccination therapy for patients with spontaneous recurrent abortion;
 - 3) Collection and preservation of peripheral blood stem cells for transplantation;
 - 4) Dendritic cell-based cancer immunotherapy.
 - 5) Anti-angiogenic cancer therapy.

Teaching activities

Sixth-year 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 3 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 and their importance in transfusion medicine;
- 3) Methodology of blood typing and compatibility typing 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) The indications and techniques of autologous blood collection and preservation;
- 7) The techniques for peripheral blood stem cells (PBSCs) collection and preservation, as well as their clinical application;
- 8) The immunotherapy of cancer patients;
- 9) The recent advances in the field of blood transfusion, including the “New Blood Law”, and the recently revised “Indications of blood

products” and “The principles of transfusion practice”.

- 10) One-day visit to the Japanese Red Cross Blood Center, to learn the general process of blood donation and transfusion, including the types of blood products, and their indications.

Research activities

Research on red cells, leukocytes, and platelets, the post-transfusional complications, transplantation immunology, immunotherapy, and stem cell biology are the main themes of the department. Typing of blood cells is performed by serological and DNA-based methods. The HLA typing, which was introduced by ex-Professor Takeo Juji, one of the pioneers of this field, is an essential test for 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 Professor Yoichi Shibata, the previous professor, and its applicability is now extended for granulocyte as well as endothelial cell serology. Transplantation immunology, including stem cell biology, and development of immunotherapeutic strategies to treat cancer patients and patients with recurrent abortion are also being performed. Recently, development of new materials for medical use is being researched. 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.
4. Study on the mechanisms of transfusion-associated GVHD and its prevention.
5. Development of a new methodology for platelet cross-match.
6. Detection and characterization of anti-endothelial cell antibodies, and study on their role in the pathogenesis of inflammatory and autoimmune diseases, as well as in organ transplantation.

7. HLA and HPA genotyping.
8. Development of a new methodology for evaluation of platelet function.
9. Development of new strategies for the treatment of cancer patients, by targeting the tumor vasculature.
10. Dendritic cell-based immunotherapy of cancer patients.
11. Ex-vivo expansion of hematopoietic stem cells and their clinical application.
12. 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 one professor, one associate professor and three lecturers. 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 also perform minimal access surgery for endometriosis, uterine fibroid, benign tumor and so on.

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 nineteen 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 the field of gynecological surgery, we have been constantly trying to minimize surgical invasion to patients as much as possible. With both of well-equipped instruments and well-trained expertise, more than 90% of surgery cases for benign gynecological disorders are operated endoscopically. These endoscopic surgeries include laparoscopic or laparoscopically assisted cytotectomy or salpingo-oophorectomy, laparoscopic hysterectomy or laparoscopically assisted vaginal hysterectomy, laparoscopic or laparoscopically assisted myomectomy, diagnostic laparoscopy for infertility, laparoscopic surgery for ectopic pregnancy, hysteroscopic surgery and so on, which make a total of about 400 cases per year.

Primary care peri/post-menopausal women is becoming more important. We have already established the primary care system for women focusing on climacteric syndrome and osteoporosis. Hormone replacement therapy (HRT) is employed for the purpose.

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 of endometriosis, 4) effect of ovarian steroid hormones on bone metabolism, and 6) 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 associate professor and one lecturer, being directed practically by Professor Yuji Taketani, the Chairman of the Department of Obstetrics and Gynecology. The staff members are taking part in both clinical and research activities, as well as teaching activities, with 18 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 uterine cervical cancer has been investigated these two decades. To identify the risk factors for cervical intraepithelial neoplasia (CIN), we reanalysed the data from our previous case-control study by adjusting for human papillomavirus (HPV) antibodies. Unlike our previous study based only on HPV DNA, smoking and Chlamydia trachomatis infection were revealed as significant risk factors for CIN after adjustment for HPV antibodies. The enhanced oncogenicity of particular human papillomavirus type 16 (HPV16) E6 variants is population-dependent, implying the involvement of additional genetic cofactors. This study was designed to investigate the association between E6 variants and human leukocyte antigen (HLA) polymorphism within a Japanese population.

Fifty-seven women with HPV16-positive cervical cancer were analyzed for E6 sequence variation and its relationship to HLA class II alleles. Compared with local controls (n = 138) and published controls (n = 916), DRB1*1501 and DQB1*0602 frequencies were significantly increased among patients with HPV16 E6 prototype (n = 11). Additionally, DRB1*1502 was positively associated with a particular E6 variant designated D25E (n = 25), although we could not find a significant association between HLA class II alleles and L83V variants (n = 16). Our observations suggest that a specific match between E6 variant proteins and HLA types may contribute to HPV16-related cervical carcinogenesis.

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.

We also investigated interacting proteins with the HPV E6 protein. Recently, a LAP protein, scribble, was identified in *Drosophila* epithelia as a basolateral protein that controls the apical-basolateral polarity. Loss of scribble causes disorganisation and overgrowth of the epithelia. Scribble has a human homologue, human scribble (hScrib), which is a substrate of ubiquitin-mediated degradation by human papillomavirus E6 and the E6AP ubiquitin-protein ligase. In the present study, we revealed that hScrib localised to the basolateral regions of the epithelial cell line MDCK and human uterine cervical epithelial tissues by immunofluorescence. Human scribble colocalised rather with the adherens junction protein E-cadherin, but not with the tight junction protein ZO-1. Histochemical analysis showed a dramatic decrease in the expression of hScrib with the progression of disease from normal uterine cervical tissues to invasive cervical cancers through the precursor lesions. In contrast, the expression of hScrib

was retained in the throughout epithelial layer of the HPV-negative cervical high-grade squamous intraepithelial lesions (H-SIL). Although quantitative RT-PCR revealed no significant downregulation of hScrib mRNA expression in the H-SIL, it revealed a clear downregulation in the invasive cancers. These results suggest the possibility that degradation by HPV E6 is one of the causal roles for the progressive decrease of hScrib expression during the disease progression from low-grade squamous intraepithelial lesions to H-SIL, and a cooperative role of downregulation of hScrib mRNA expression and ubiquitin-mediated degradation of hScrib by E6 and E6AP led to the complete decrease of hScrib expression during the process of carcinogenesis from H-SIL to invasive cancer. These data underscore the importance of hScrib in the construction of tissue architecture and prevention of cancer development.

Another basic research is focused on analysis of tumor suppressor genes in gynecological malignancies as following.

1 Human Scribble

Recently, a LAP protein, scribble, was identified in *Drosophila* epithelia as a basolateral protein that controls the apical-basolateral polarity. Loss of scribble causes disorganisation and overgrowth of the epithelia. Scribble has a human homologue, human scribble (hScrib), which is a substrate of ubiquitin-mediated degradation by human papillomavirus E6 and the E6AP ubiquitin-protein ligase. In the present study, we re-vealed that hScrib localised to the basolateral regions of the epithelial cell line MDCK and human uterine cervical epithelial tissues by immunofluorescence. Human scribble colocalised rather with the adherens junction protein E-cadherin, but not with the tight junction protein ZO-1. Histochemical analysis showed a dramatic decrease in the expression of hScrib with the progression of disease from normal uterine cervical tissues to invasive cervical cancers through the precursor lesions. In contrast, the expression of hScrib was retained in the throughout epithelial layer of the HPV-negative cervical high-grade squamous intraepithelial lesions (H-SIL). Although quantitative RT-PCR revealed no significant downregulation of hScrib mRNA expression in the H-SIL, it revealed a clear downregulation in the invasive cancers. These results

suggest the possibility that degradation by HPV E6 is one of the causal roles for the progressive decrease of hScrib expression during the disease progression from low-grade squamous intraepithelial lesions to H-SIL, and a cooperative role of downregulation of hScrib mRNA expression and ubiquitin-mediated degradation of hScrib by E6 and E6AP led to the complete decrease of hScrib expression during the process of carcinogenesis from H-SIL to invasive cancer. These data underscore the importance of hScrib in the construction of tissue architecture and prevention of cancer development.

Drosophila discs large (Dlg) is one of neoplastic tumor suppressors, which genetically links to scribble. E6 also targets human Dlg (hDlg) for ubiquitin-mediated degradation. Ubiquitin-protein ligase involved in this process has not been identified thus far. Here we investigated mechanism underlying degradation of three target proteins of E6, hScrib, hDlg, and p53 by using eighteen HPV 16 E6 mutants with single amino acid substitution. In vitro degradation ability of each E6 mutant was equivalent for these tumor suppressors. We investigated whether E6AP is involved in ubiquitin-mediated degradation of hDlg. In vitro binding assay revealed that hDlg formed ternary complex with E6-E6AP complex. The ability of E6 mutants to degrade these tumor suppressors was correlated with their ability to interact with E6AP. Furthermore, hDlg was targeted for in vitro ubiquitination in the presence of both E6 and E6AP. These data revealed that E6AP is extensively involved in the ubiquitin-mediated degradation of E6-dependent substrates as a cellular E3 ubiquitin-protein ligase.

Human Scribble, classified as a LAP protein containing leucine-rich repeats and PDZ domains, interacts with E6 through its PDZ domains and C-terminal PDZ domain-binding motif of E6 protein. Interaction between human Discs Large (hDlg), which is a substrate of E6 for the ubiquitin-mediated degradation, and adenomatous polyposis coli (APC) has been shown. Here, we investigated whether hScrib and APC interact with each other in vitro and in vivo. Interaction between hScrib and APC is mediated by the PDZ domains 1 and 4 of hScrib and C-terminal PDZ domain-binding motif of APC. Human Scribble co-localized with APC at the synaptic sites of

hippocampal neuron and at the tip of membrane protrusion in the epithelial cell line. Interference of the interaction between hScrib and APC caused disruption of adherens junction. Knockdown of hScrib expression by RNAi disrupts localization of APC at the adherens junction. These data suggest that hScrib may participate in the hDlg-APC complex through its PDZ domains and regulate cell cycle and neural function by associating with APC.

Drosophila tumor suppressor Scribble has been identified as an apical-basolateral polarity determinant in epithelia. A human homolog of *Drosophila* Scribble, human Scribble (hScrib), has been identified as a protein targeted by human papillomavirus E6 for the ubiquitin-mediated degradation dependent on E6AP, a cellular ubiquitin-protein ligase. Human Scribble is classified as a LAP protein, having leucine-rich repeats (LRRs) and PDZ domains. We investigated whether hScrib, which is thought to have a role in polarity determination based on the data of its *Drosophila* homolog, is involved in cell-cycle regulation and proliferation control of epithelia. Transfection of hScrib inhibits cell-cycle progression from G1 to S phase, and it up- and down-regulates expression of adenomatous polyposis coli and cyclins A and D1, respectively. Knockdown of hScrib expression by siRNA leads to cell-cycle progression from G1 to S phase. We explored functional domain mapping to reveal which domains of hScrib are critical for its cellular proliferation control and localization at the basolateral membrane. We found that LRRs and PDZ domain 1 are indispensable for hScrib to inhibit cell growth by blocking cell-cycle progression and to keep its proper localization. These data indicate that basolateral membrane localization of hScrib is closely related to its proliferation control. Our findings suggest the possibility that hScrib is involved in signal transduction to negatively regulate cell proliferation by localizing at the basolateral membrane of epithelial cells through LRRs and PDZ domains.

We also investigated which E3 ubiquitin-protein ligase is involved in the ubiquitin-mediated degradation of hDlg. Human scribble (hScrib), which was identified as sub-strate of human papillomavirus (HPV) E6 for ubiquitin-mediated degradation dependent on ubiquitin-protein ligase E6AP, is a

human homolog of *Drosophila* neoplastic tumor suppressor scribble, in which mutation causes loss of polarity and overgrowth of epithelia. *Drosophila* discs large (Dlg) is one of neoplastic tumor suppressors, which genetically links to scribble. E6 also targets human Dlg (hDlg) for ubiquitin-mediated degradation. Ubiquitin-protein ligase involved in this process has not been identified thus far. Here we investigated mechanism underlying degradation of three target proteins of E6, hScrib, hDlg, and p53 by using eighteen HPV 16 E6 mutants with single amino acid substitution. In vitro degradation ability of each E6 mutant was equivalent for these tumor suppressors. We investigated whether E6AP is involved in ubiquitin-mediated degradation of hDlg. In vitro binding assay revealed that hDlg formed ternary complex with E6-E6AP complex. The ability of E6 mutants to degrade these tumor suppressors was correlated with their ability to interact with E6AP. Furthermore, hDlg was targeted for in vitro ubiquitination in the presence of both E6 and E6AP. These data revealed that E6AP is extensively involved in the ubiquitin-mediated degradation of E6-dependent substrates as a cellular E3 ubiquitin-protein ligase. hScrib, human homologue of *Drosophila* neoplastic tumor suppressor, was identified as a target of human papillomavirus E6 oncoprotein for the ubiquitin-mediated degradation. Here, we report that hScrib is a novel death substrate targeted by caspase. Full-length hScrib was cleaved by caspase during death ligands-induced apoptosis, which generates a p170 C-terminal fragments in HeLa cells. In vitro cleavage assay using recombinant caspases showed that hScrib is cleaved by the executioner caspases. DNA damage-induced apoptosis caused loss of expression of full-length hScrib, which was recovered by addition of caspase-3 inhibitor in HaCat cells. TUNEL positive apoptotic cells, which were identified 4 hours after UV irradiation in HaCat cells, showed loss of hScrib expression at the adherens junction. Mutational analysis identified the caspase dependent cleavage site of hScrib at the position of Asp-504. While MDCK cells transfected with GFP-fused wild type hScrib showed loss of E-cadherin expression and shrinkage of cytoplasm by UV irradiation, cells transfected with hScrib with Ala substitution of Asp-504 showed

resistance to caspase dependent cleavage of hScrib and intact expression of E-cadherin. These results indicate that caspase dependent cleavage of hScrib is a critical step for detachment of cell contact during process of apoptosis.

2 PTEN

Although the mutation of PTEN, a tumor suppressor, is known to be involved in tumorigenesis of endometrioid adenocarcinomas of the endometrium and ovary, the role of PTEN alteration in endometrioid adenocarcinoma of the cervix remains to be investigated. To elucidate the molecular pathogenesis of cervical adenocarcinoma and adenosquamous carcinoma, and in particular to examine the potential role of PTEN mutation in endometrioid-type cancer of the cervix, we analyzed 32 cervical adeno- or adenosquamous carcinomas (8 endometrioid adenocarcinomas, 14 mucinous adenocarcinomas and 10 adenosquamous carcinomas) for PTEN mutations and HPV infections. PTEN mutation was detected in 2 of 8 (25.0%) endometrioid cases, 2 of 14 (14.3%) mucinous cases, and none of 10 (0%) adenosquamous cases. HPV DNA was detected in 11 out of 18 (61.1%) PTEN wild-type adenocarcinomas and 8 out of 10 (80.0%) adenosquamous carcinomas. Among 11 HPV-negative adenocarcinomas, 40.0% (2/5) endometrioid cases and 33.3% (2/6) mucinous cases were shown to be PTEN mutated, while no cases (0/21) were PTEN-mutant in the remainder (i.e. adenosquamous carcinomas and HPV-positive adenocarcinomas). The current observations suggest that PTEN mutation is frequently detected in HPV-negative adenocarcinomas of the cervix and the most prevalent occurrence of PTEN mutation in endometrioid subtype is keeping with endometrial and ovarian carcinomas.

Next, we analyzed involvement of PTEN in treatment of endometrial cancer. Young patients with complex atypical hyperplasia (CAH) or stage Ia, G1 adenocarcinoma (IaG1) of the endometrium, who desire to preserve fertility, can select the conservative therapy by oral progestin, medroxyprogesterone acetate (MPA). However, conservative treatments involve potential risks of progression and recurrence. In an attempt to find out molecular markers for sensitivity to MPA, we performed immunohistochemical analysis of PTEN, phospho-Akt, p53, ER

and PgR in MPA-treated 31 cases with CAH or IaG1. Eleven of 12 cases (92%) with CAH and 15 of 19 cases (79%) with IaG1 demonstrated an initial complete response, while five patients underwent hysterectomy due to no response. Four of 11 responders (36%) with CAH and five of 15 responders (33%) with IaG1 later developed relapse. Five of nine patients (56%) with CAH and three of 11 patients (27%) with IaG1 became pregnant after infertility treatment. Immunohistochemical analysis revealed that phospho-Akt expression was significantly decreased by MPA administration ($p=0.002$). Furthermore, combination of two factors, weak phospho-Akt or PTEN-null expression, was found to be significantly associated with receiving hysterectomy ($p=0.04$), while each factor showed a trend without statistical significance ($p=0.07$ and 0.2 , respectively). Strong expression of both ER and PgR significantly correlated with successful pregnancy after infertility treatment following complete response to MPA ($p=0.02$). Our observations *in vivo* suggest that anti-tumor action of MPA may be mediated by dephosphorylation of Akt, and that immunohistochemical evaluation of phospho-Akt and PTEN may be able to predict the outcome of MPA therapy.

3 SFRP1 gene

The SFRP1 gene on chromosome 8p11.2 encodes a Wnt signaling antagonist, and was recently demonstrated to be a new tumor suppressor that is inactivated by promoter methylation in human colon cancers. Here, we analyzed promoter methylation of the SFRP1 gene in human ovarian cancers, in which loss of heterozygosity in 8p is frequently observed and involvement of the Wnt signaling pathway has been suggested. Methylation-specific PCR (MSP) analysis showed that four of 13 ovarian cancer cell lines and two of 17 primary ovarian cancers had methylated SFRP1, while an immortalized ovarian epithelial cell line, HOSE, and seven ovarian endometrial cyst samples did not. In the four ovarian cancer cell lines with the methylation, SFRP1 was not expressed at all as determined by quantitative RT-PCR analysis. These results show that SFRP1 is inactivated by promoter methylation in human ovarian cancers, as well as colon cancers.

4 hMSH2

The DNA mismatch repair gene is a key regulator in the elimination of base-base mismatches and insertion/deletion loops (IDLs). Human MutS homologue 2 (hMSH2), originally identified as a human homologue of the bacterial MutS, is a tumour suppressor gene frequently mutated in hereditary non-polyposis co-rectal cancer. Hereditary non-polyposis colorectal cancer is characterised by the early onset of colorectal cancer and the development of extracolonic cancers such as endometrial, ovarian, and urological cancers. Oestrogen receptor (ER) alpha and beta are members of a nuclear receptor (NR) superfamily. Ligand-dependent transcription of ER is regulated by the p160 steroid receptor coactivator family, the thyroid hormone receptor-associated proteins/the vitamin D receptor-interacting proteins (TRAP/DRIP) mediator complex, and the TATA box-binding protein (TBP)-free TBP associated factor complex (TFTC) type histone acetyltransferase complex. We identified the interaction between ER alpha/beta and hMSH2. Immunoprecipitation and glutathione-S-transferase pull-down assay revealed that ER alpha and hMSH2 interacted in a ligand-dependent manner, whereas ER beta and hMSH2 interacted in a ligand-independent manner. Oestrogen receptor alpha/beta bound to hMSH2 through the hMSH3/hMSH6 interaction domain of hMSH2. In a transient expression assay, hMSH2 potentiated the transactivation function of liganded ER alpha, but not that of ER beta. These results suggest that hMSH2 may play an important role as a putative coactivator in ER alpha dependent gene expression.

(2) Clinical oncology

To compare treatment outcome results of conventional surgery vs. radiotherapy (RT) for carcinoma of the uterine cervix. A retrospective analysis was conducted of 152 patients with uterine cervical cancer radically treated with surgery or high dose-rate intracavitary brachytherapy (HDR-ICBT) with or without external RT from June 1991 to May 2004. The median follow-up time was 43.5 months (range, 1.0-130.0 months). The median age was 53 years (range, 25-81 years). There were 13 patients (9%) in stage IA, 52 (34%) in stage IB, 24 (16%) in stage IIA,

and 63 (41%) in stage IIB. The conventional surgery group included 115 patients (76%) who underwent hysterectomy with pelvic lymph node dissection. Of these, 72 (63%) received postoperative radiotherapy. Thirty-seven patients (24%) were assigned to the RT group. Of these, 14 (38%) received chemoradiotherapy. Three patients with stage I received ICBT-alone without external beam irradiation. RESULTS: The 5-year cause-specific survival (CSS) rates for surgery and RT were 79.9% and 82.3%, respectively; the difference between these two treatments was not statistically significant ($P = 0.8524$). The differences in the survival rates between the two treatments for each of the stage I or stage II patients were also not statistically significant ($P = 0.8407$ for stage I and $P = 0.6418$ for stage II). This retrospective study suggests that RT results in compatible survival with conventional surgery for patients with stage I-II cervical carcinoma.

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Organization

The Department of Perinatal Medicine is organized by one professor and one associate professor and one lecturer, being directed practically by Professor Yuji Taketani, 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 15 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 subjects of studies were focused on “fetus” and “ultrasound” in perinatology and medical engineering research group.

Fetal behavior, particularly breathing movements and sleep-wakefulness cycle were studied with ultrasound in human fetuses. Studies were done to investigate mechanism of fetal brain damage by repeated cord occlusion in sheep. The effect of brain damage on fetal behavior was also studied.

Recurrent spontaneous abortion (RSA) is diagnosed by a history of three times or more spontaneous abortions in the first trimester. Our “RSA clinic” opens once a week. About 200 new couples with RSA visit our hospital in a year. The patients are checked several risk factors of RSA, such as anatomical, chromosomal, hormonal, biological, or autoimmune factors. To RSA patients with autoimmune factors, especially with antiphospholipid antibodies, anticoagulation therapy is performed. For the low risk group, low dose aspirin is administered. Heparin injection is performed for the 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. Further to RSA patients with unknown etiology, the immunotherapy with her husband’s lymphocyte inoculation had been indicated. The inoculation was usually performed four to six times in every two or three weeks. In our clinic, after the immunotherapy, their pregnancy outcomes had extremely improved. The successful reproductive rate had achieved about 75%.

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Reproductive, Developmental and Aging Sciences

2. Pediatric Sciences

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(As of March 31, 2011)

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Introduction and Organization

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

Our staff consists of 1 professor, 2 associate professors, 2 lecturers, 18 associate professors, 17 senior residents, 2 research fellow, and 19 graduate students on March 31, 2009.

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, Ewing sarcoma, osteosarcoma, brain tumors, etc.), cardiac disorders (congenital heart diseases and Kawasaki disease), neuromuscular disorders, immunological/allergic disorders (common variable immunodeficiency, chronic granulomatous disease and bronchial asthma), renal and urinary tract diseases (nephrotic syndrome, chronic glomerulonephritis, purpura nephritis and renal and/or urinary tract anomalies), endocrinological disorders, metabolic disorders and psychosomatic diseases are admitted in the wards. Approximately 10 patients received hematopoietic stem cell transplantation every year. There are patients with severe combined immunodeficiency, aplastic anemia-myelodysplastic syndrome, acute lymphocytic leukemia with high-risk features, acute myelogenous leukemia, non-Hodgkin lymphomas, disseminated neuroblastoma and brain tumors.

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 in April, 2006.

(As of March 31, 2009)

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, immunology, allergy, pulmonology and neonatology. We also have multidisciplinary research groups and laboratories such as cell biology, genetic molecular biology and epidemiology. The main subjects of research during the last year are listed as follows.

- ① Hematology/Oncology group: We discovered another mechanism of aberrant ALK activation observed in a neuroblastoma-derived cell line, NB-1, in which a short formal ALK protein having a truncated extra-cellular domain. Several novel mutations of IDH1/2 were detected in pediatric solid tumors including neuroblastoma, rhabdomyosarcoma, and Ewing sarcoma. Functional impact of these mutations was currently analyzed by a high-throughput metabolome study.
- ② Nephrology group: We analyzed clinical features and pathophysiological findings of nine EPS-FTNS patients with MYH9 mutations, and found the novel role of NMMHC-IIA in the development of FSGS.
- ③ Cardiology group: A novel intervention catheter technique in PDA was applied in several congenital heart disease patients.
- ④ Immunology group: Research area of interest includes refractory Kawasaki disease and epidemiology of childhood infectious disease.
- ⑤ Neonatology group: We conducted a research on the establishment of the methods of newborn

screening system about the patients of congenital cytomegalovirus infection. Also a trial of making new artificial milk contains less protein equivalent of human milk.

- ⑥ Neurology Group: The pathogenetic mechanism of acute encephalopathy as well as genetic basis of congenital CNS anomalies is investigated. The neuropathological studies of perinatal brain damage, in particular periventricular leukomalacia, is also performed.
- ⑦ Endocrinology and Metabolism group: Molecular analyses of genes involved in hereditary rickets and a novel insight in their functional consequences are studied. Genetic factors for vitamin D deficiency are analyzed.

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Department of Pediatric Surgery

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History and organization

In 1951, a pediatric surgical team was established in the Department of Second Surgery. Subsequently, in 1961, a pediatric surgical research team, which would eventually research diaphragmatic hernia, was established with a chief, Dr. Ishida, by Professor Kimoto.

In 1971, it was authorized as the first clinical department of Pediatric Surgery in a National University.

A pediatric intensive care unit was founded with Prof. Ishida in 1973, and a ward which could accommodate mainly pediatric surgical patients was completed.

Assistant Prof. Saito assumed office as the first Director of this Pediatric Surgery clinical department.

Dr. Sumio Saito became Professor of Pediatric Surgery in 1983. Professor Saito had enthusiastically performed clinical studies such as operation techniques and the use of biliary atresia.

Dr. Nakajo took office as a professor in 1985. Prof. Nakajo had 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 been inherited by pediatric surgeons as Nakajo methods.

Our department was authorized as the Department of

Pediatric Surgery in 1989 after Kyusyu University by the Ministry of Education.

Dr. Yoshiaki Tsuchida assumed the role of Professor in 1990 and published many highly regarded articles, mainly concerning neuroblastoma and Wilm's tumor from research and clinical work.

In 1995, the department was reorganized as the Reproductive, Developmental and Aging Science, Pediatric Science and Pediatric Surgery, due to the University policy for the Graduate School.

In 1997, Dr Hashizume became Professor in the Department of Pediatric Surgery. He started 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. The present staffs are the chief professor, one associate professor, one lecturer, four research associates, two senior residents, and three graduate students. More than 20 members of our department shoulder the clinical work as pediatric surgeons.

Clinical activities

Staffs higher than research associate level take charge of the out-patient 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 has opened with careful detailed explanations and this has received a favorable reception.

Our ward is on the second floor south of the hospital A wing. Other pediatric surgical patients are also admitted to this ward. We have 16 beds in the ward and about 400 patients a year are hospitalized. Most operation cases are inguinal hernia, but we have 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, trachea stenosis, and lung cysts.

We compare positively with Pediatric Surgery at other institutions that perform endoscopic surgery (laparoscopic surgery/thoroscopic surgery). We have developed an endoscopic surgery technique for pediatric diseases not covered by insurance to apply to advanced medical care. Furthermore, we surgically manage seriously ill mentally and physically handicapped infants and nervous system intractable disease patients to improve their quality of life, and we cooperate with pediatricians (neonatologists) to treat patients with prenatal diagnosis

Education

We expose 1st and 2nd year students to our daily clinical work as well as research work during “Free Quarter” and “Research Lab Visit” courses. These students are guided to be concerned with clinical areas and are in charge of part of the research project. The students hold a results announcement party at the end of training. For M2 students, general pediatric surgery and neonatal surgery instruction is given by the professor and the lecturer.

An education program is also provided for M3 and M4 students for 5 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 include the practice of cardiac massage and intra-tracheal intubation using mannequins for practice.

We take charge of the core surgical curriculum in 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.

Research activities

Professor Iwanaka has established a low invasive operation study group and developed experiments for endoscopic surgery using white rabbits in the animal resources research facilities. This study group tries to develop endoscopic surgery for infants. Prof. Iwanaka also provides a training program for infant endoscopic surgery for members of our department. In addition, he has started the project of robotic surgery to perform radical operation with laparoscopic surgery technique for biliary atresia. This group creates multiple functional forceps 3 mm in a diameter for robotic surgery system at first. And they are developing radical operation for long gap esophageal atresia by using the latest technique of NOTES (Natural Orifice Transluminal Endoscopic Surgery).

The intestinal tract immunity study group was the first to start infant digestive organ function activation medical treatment using a probiotic, Shinbiotic, with good clinical effects. Further more inspection is performed in order to do randomized control study in clinical course.

Professor Iwanka has performed the study of the regenerative medicine positively. He founded a new laboratory in the Department of Tissue Engineering to perform not only conventional animal experiments but also human experiments to fabricate a trachea in the clinical course.

The tumor study group analyzes the genes related to tumor development and suppression. Further more, new tumor marker is studying by using tumor tissues and blood samples.

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Reproductive, Developmental and Aging Sciences

3. Aging Sciences

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Introduction and Organization

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

Since elderly patients usually have multiple organ disorders, we have to take care of the patients as a whole from multiple points of view. In addition, in the elderly patients, symptoms, signs and responses to the treatment are sometimes quite different from the young. We have to have a broad knowledge on the physiological and metabolic changes with aging when we treat the elderly patients. Quality of life of the patients is another point of view which should be emphasized.

Our sub-specialty includes respirology, cardiology, neurology, hematology, endocrinology, and bone metabolism, besides the general geriatric internal medicine.

We are trying to elucidate the pathophysiology of aging process and 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 around 25 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 resident 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. 354 new and a total of 19,250 patients visited the out-patient clinic in a 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

- 1) Research on the molecular mechanism of vascular calcification
 - i) Molecular biology of vascular calcification in vitro
 - ii) Animal model of vascular calcification
 - iii) Clinical factors associated with vascular calcification
- 2) Regulation of vascular function by sex hormone
- 3) Molecular biology for the control of aging. Cellular senescence and Sirt1 in vascular cells
- 4) Clinical association of androgen with functional decline in the elderly
- 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) Diagnosis and treatment of the demented patients
- 8) Expression and regulation of nuclear receptors in osteoblast and osteoclast
- 9) Molecular mechanism under the treatment of osteoporosis
- 10) Genetic analysis of osteoporosis and osteoarthritis
- 11) Identification and functional analysis of the target gene networks associated with hormone responsiveness in prostate and breast cancers
- 12) Role of nuclear receptors in senescence and carcinogenesis
- 13) Diagnosis and prevention of aspiration pneumonia
- 14) Novel roles of antimicrobial peptide, defensin
- 15) Adrenomedullin and airway hyperresponsiveness
- 16) Klotho protein and vitamin D in lung
- 17) Clinical investigation of sleep-related breathing disorder

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Surgical Sciences

1. Surgery

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History

Clinical and basic researches of the thoracic surgery have been performed since the prewar era in this university, when Professor Tsuduki, Masao adopted the modified Coryllos's thoracoplasty for the treatment of the pulmonary tuberculosis in 1934. They initiated thoracoscopy for the treatment of the tuberculosis in our country. After the successful application of the antituberculous drugs, surgical treatment of the thoracic malignant neoplasms was the major concern of the thoracic surgery.

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).

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 improve 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

Three staffs (Nakajima J, Murakawa T, and Sano A), 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 of the diseases of the respiratory and the mediastinal organs and the chest wall, except for diseases of the esophagus and mammary glands. Approximately 330 surgeries are performed in the department in 2010.

Primary lung cancer has been the leading cause of death among the malignant neoplasms in our country. Basic and clinical investigations for the treatment of lung cancer are very important, because number of the patients who died of the lung cancer has been increasing. In our department, the staffs are engaging the clinical works, studies and educations of diagnostics and therapeutics of the lung cancer and other thoracic diseases.

We have performed the modern-style thoracoscopy for the diagnosis and treatment of the thoracic disease with less surgical invasiveness since 1992. Approximately a half of the surgical procedures in our department have been safely and successfully accomplished through thoracoscopy. Researches on

less-invasiveness, oncological advantage of the thoroscopic surgery have been studied actively.

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.

Thymic epithelial neoplasms, such as thymoma and thymic carcinoma, show broad spectrum in the degree of malignancy. They also associated with paraneoplastic syndromes, such as the myasthenia gravis and the pure red cell aplasia. We have 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.

Adoptive immunotherapy with activated autologous gammadelta T-cell for the patients with recurrent lung cancer or pulmonary metastasis from colorectal cancer is performed as a clinical study to investigate the safety and anticancer effect of this immunotherapy.

We are now preparing for clinical lung transplantation for the patients suffering from advanced stage of diffuse lung diseases that are refractory to conventional treatments.

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. The Department of Thoracic Surgery also offers the 4-year postgraduate program for qualified surgeons who are willing to specialize in the thoracic surgery.

Current researches

Main subjects of current research at present include basic and clinical studies on the malignant neoplasms in the thorax, transplantation of the thoracic organs and the cryopreserved tissues. Recently we conducted clinical studies on the immunotherapy with adopted gamma- delta- T-cell for the treatment of the advanced

non-small cell lung cancer and the pulmonary metastasis from extrathoracic organs.

We are now preparing clinical lung transplantation program in this hospital with the usage of lungs from brain-dead donors.

The following are the major themes under research:

- (1) Minimally invasive surgeries for thoracic malignant neoplasms.
- (2) Analysis of the factors influencing the prognosis of lung cancer or mediastinal neoplasms.
- (3) Global analysis of oncogenes and suppressor genes associated with lung cancer.
- (4) Clinical trial and basic research on adoptive anticancer immunity of the autologous gamma-delta-T-cell for the treatment of the recurrent primary lung cancer or pulmonary metastasis from colorectal cancer.
- (5) Clinical trial of vaccine immunotherapy for the recurrent non-small cell lung cancer.
- (6) Analysis on mechanisms of acute or chronic rejection of the allogeneic lung and trachea.

Selected publications

- (1) Nakajima J, Murakawa T, Fukami T, Goto S, Kaneko T, Yoshida Y, Takamoto S, Kazuhiro K. A phase I study of adoptive immunotherapy for recurrent non-small cell lung cancer patients with autologous gammadelta T cells. *Eur J Cardio-Thorac Surg* 2010; 37:1191-7
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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. Present staffs are one Chief Professor, one Associate Professor and two Lecturer and six Associates.

Clinical Activities

Clinical conference starts at 7:15 am in weekdays. Regular surgery is scheduled on Monday, Wednesday, Thursday 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 350, 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 aortic valve sparing root replacement, arch replacement using retrograde cerebral perfusion, treatment of extended thoracic aortic aneurysm, ventricular assist device implantation, off- pump coronary artery bypass surgery, mitral valve plasty and repair of complex congenital heart diseases, such as Jatene, Fontan and Norwood operations.

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 2011, 15 cases of heart transplantation and 71 cases of ventricular assist device implantation were performed in The University Hospital.

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, 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) etiological approach to diabetic retinopathy and ischemic heart disease, 3) basic and clinical research on cryopreserved allograft, 4) new effective brain and spinal cord protection strategy, 5) a new technique of aortic valve sparing root replacement and its hemodynamic evaluation, 6) mechanism analysis of right heart failure and development of effective

pharmacological therapy, 7) application of regenerative medicine to end-stage heart failure, 8) development of new heart preserving solution .

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Department of Gastrointestinal Surgery

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Homepage

General Affairs:

Since 2001, 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. The Department of Gastrointestinal Surgery presently comprises one Professor, one Lecturer, one Hospital Lecturer and nine associates.

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:

We educate chief residents and junior residents in rotation. Our educational systems for residents and students reflect our aforementioned principles. Medical students are encouraged to be members of clinical staffs rather than mere students during their bedside

Learning. They learn generic 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.

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:

The main research activities of the department of Gastrointestinal Surgery are 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. Current research topics are:

1) Carcinogenesis of gastrointestinal cancer

- Diversity of gastrointestinal carcinogenesis
- Gender differences in gastrointestinal cancers
- Roles of sex hormones in gastrointestinal carcinogenesis
- Monoclonality of intestinal metaplasia
- Roles of *Helicobacter pylori* infection in gastric

carcinogenesis

- Interaction between cancer and interstitial tissue
- Experimental evaluation of promotive mechanisms of gastroduodenal reflux and denervation of the gastric mucosa in gastric remnant carcinogenesis
- Preventative roles of PPAR γ in gastric carcinogenesis
- Clinical and experimental studies on the Barrett esophagus

2) Molecular mechanisms of gastrointestinal tract cancer

- Role of bone marrow derived progenitor cells in gastric carcinogenesis
- Apoptosis-related molecules during multimodal therapies for esophageal cancer
- Angiogenic factors in gastrointestinal tract cancer
- Genetic alterations in gastric cancer and colorectal cancer
- Methylation status of gastrointestinal cancers
- Lymph node micrometastasis of gastric cancer

3) Minimally invasive surgery for the treatment of early cancer of the stomach and large intestine

- Endoscopic treatment
- Laparoscopic surgery
- Optimal scope of lymphadenectomy
- Sentinel lymph node navigation surgery for early gastric cancer
- Evaluation of postoperative QOL after pylorus preserving gastrectomy (PPG) and jejunal interposition for early gastric cancer

4) Alternative surgical design for the improvement of the patient's postoperative quality of life

5) Radical treatment for advanced gastric cancer

6) Multimodal treatment for gastrointestinal tract cancer

- Neoadjuvant or definitive chemoradiation therapy for esophageal cancer
- Neoadjuvant or adjuvant chemotherapy for gastric and colorectal cancer

7) Gastrointestinal motility

- Mechanism of peppermint oil solution of digestive tract
- Role of cytokine and COX-2 in gastrointestinal motility
- Manipulation of the intestine and postoperative motility

Clinical Activities:

We have outpatient clinics from Monday through Friday. We have specialized divisions for outpatient management of esophageal, gastric, and colorectal 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. Ordinarily, each subgroup takes care of 10-12 patients.

We have our own multidisciplinary disease evaluation systems for inpatients and outpatients, such as endoscopy and endoscopic ultrasonography for upper and lower gastrointestinal tracts, ultrasound diagnosis, and barium roentgenogram. These multidisciplinary services provide good opportunities to evaluate the diseases systematically from the surgeon's standpoint. We also perform endoscopic treatment, especially mucosal resection for strictly selected early cancers in the upper and lower gastrointestinal tract.

The weekly official activities of our department are Ward Rounds by the Professor on Monday and by the Associate Professor on Friday. We have post- and preoperative case conferences on Tuesday, Wednesday and Thursday morning, respectively, and a journal club on Monday. We also have a specialized upper gastrointestinal case conference on Tuesday evening. Nursing-staffs have meetings with medical doctors on every Friday to ensure a high quality of patient care during the patients' hospital stay.

Generally, elective surgery is scheduled on Tuesday, Wednesday and Thursday. The statistics for 2005 show more than 250 cases of elective surgery and emergency surgery. 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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Department of Hepatobiliary Pancreatic Surgery and Department of Artificial Organ and Transplantation Surgery

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Organization

We specialize in hepato-pancreato-biliary surgery and liver transplantation. The Hepatobiliary Pancreatic Surgery Division and Artificial Organ and Transplantation Surgery Division precede the Second Department of Surgery, which was established in 1893.

Clinical Activities

We shared around 60 beds mainly on the A9 north floor ward with hepatobiliary pancreatic surgery and transplantation division, high care unit and intensive care unit on the A4 floor. Each inpatient is taken care of by senior and junior specialist surgeons and a resident in the field of his or her disease throughout the pre- and postoperative periods. Staff members are responsible for the entire care of the patients on a 24-hour-a-day basis. Elective operations are carried out on Monday, Wednesday and Friday.

Teaching Activities

We take part in clinical lectures and bed-side teaching for medical students in cooperation with the other departments. Bed-side teaching is provided to the fifth and sixth grade students on a man-to-man basis with staff members. During a three-week period each student learns the basic way of thinking for correct diagnosis and treatment, fundamental techniques of radiological examinations and laboratory data, and pre- and postoperative patient care.

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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 robotic surgery for prostatectomy substituting open procedures.

The professor, associate professors, instructors 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.

Clinical activities

There are 44 beds in the ward (8th floor of the central-ward-building). 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 1,800 from January 2010 to December 2010.

Elective operations are performed on Tuesday and Thursday. A total of 1,446 operations were performed in 2010. The numbers of main operations are adrenalectomy 31, radical nephrectomy 32, partial nephrectomy 25, radical cystectomy 19, radical prostatectomy 73, transurethral resection of the bladder tumor (TUR-Bt) 206, transurethral resection of the prostate (TUR-P) 28, and laparoscopic surgery 55.

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 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 29,472 patient-days from January 2010 to December 2010.

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 30 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 Associate Professor, one lecturer and nine Assistants. 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. Additionally, surgical specialties in the department include the treatment of benign and

malignant disorders of the breast and management of malignancies of the gastrointestinal tract (esophageal, gastric, and colorectal). 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 upper GI tract, lower GI tract, and breast diseases. The Department was responsible for 283 surgically treated inpatients in the year of 2008. 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 and Saturday morning. Each research unit holds its own conference every week.

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 and 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 for the fiscal year of 2009, 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

At present, our department has three major research units divided according to the members' special fields. The clinical and academic interests of our department are the upper and lower gastrointestinal tract, and the breast. We also 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 of gastrointestinal cancer
- 15) Genetic analysis on sensitivity to chemotherapeutic 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

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In 1995, a new system for postgraduate education was introduced. The First Department of Surgery was reorganized to form the Department of Vascular Surgery and the Department of Surgical Oncology. The staff of the Department of Vascular Surgery consists of one Associate Professor, one lecturer, and three Associates. 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. 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 other 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) Development of a minimally invasive treatment modality for varicose veins of lower extremity using high frequency ultrasound.
- 7) Genome wide-association studies for arteriosclerosis.
- 8) Pharmacological analysis of microcirculation in in-vivo model
- 9) Mechanism of arteriogenesis in ischemic limb.
- 10) Development of a new drug delivery system for therapeutic angiogenesis
- 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.

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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, one lecturer and two assistants and two or three residents. 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, parathyroid, and adrenal gland. In addition to treatment for malignant cases of these diseases, we

perform surgical procedures for hyperfunctional diseases. We co-work with the department of endocrine internal medicine and have about 240 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 based on telomerase activity using Q-Fish.

Research Activities

Our section has been studying about the most fundamental issues to surgery, i.e., “surgical stress” which means postoperative physiological and endocrine internal reaction and “nutritional support” for the postoperative patients. These are subjects to reduce the intra- and post-operative stresses that would be risky for the patients. Our section is like a pioneer for this area in Japan and we established Japanese Society for Surgical Metabolism and Nutrition in 1965. Graduate students organize main study group and we have presentations at some international conferences each year.

The focus of our research is “surgical metabolism and nutrition” and “the body’s adaptive responses during postoperative recovery”. In addition, we have been engaged in the project of chemo-sensitivity of breast cancer and of treatment for breast tumors by high-energy ultrasound. Research details follow.

- 1) Mechanisms of cross tolerance among different stresses (endotoxin - hypoxia/ hypoxia - hypoxia) after surgery
- 2) Role of catecholamines in adaptation to surgical stresses such as endotoxemia
- 3) Bacterial translocation after anti-cancer chemotherapy
- 4) Gender difference is a modulating factor for postoperative morbidity
- 5) Measurement of endotoxin activity through Toll-like receptor 4
- 6) Role of oxygen on local and systemic protein metabolism after major surgery
- 7) Ischemic preconditioning preserves renal dysfunction after ischemia-reperfusion
- 8) Telomere-length and telomere activity in the thyroid and the breast tumors
- 9) Application of Q-Fish in diagnosis of the thyroid and the breast tumors
- 10) Chemo-sensitivity in breast cancer

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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 in our department.

The professor, one associate professor, five lecturers and nine assistants take part in inpatient and outpatient cares as well as research and teaching activities. Twenty doctors who basically belong to our department are currently out in affiliated hospitals mainly engaged in clinical works there. Additionally, five staff members are abroad at present, mainly involved in advanced research activities in cell biology and molecular biology.

Clinical Activities

In the out-patient 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. Daily discussions are made for initially consulted cases when they are rather difficult to diagnose, by all staff members including Professor and Associate Professors. Furthermore, retrospective clinical and histological discussions are held regularly, which always gives us invaluable lessons.

Concerning the in-patient 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 ten dermatologists and 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 six grade medical students, which aims at giving a general introduction for how 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.

References Activities

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

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Organization

The present faculty of the Department of Plastic and Reconstructive Surgery consists of 1 professor, 1 associate professor, 1 lecturer, 5 associates, 7 physicians, and 3 residents. There are about 100 doctors in the department, including 8 graduate school students, 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 25 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. There are about 1,356 new patients and the total number of revisiting patients are about 9,703 in a year. In the operating theater over 410 operations are achieved under general anesthesia, while in the outpatient clinic about 150 operations are achieved under local anesthesia in a year. Each week, the professor goes the round of inpatients on Wednesday morning. Preoperative and postoperative conferences and seminar that all members of the department should attend are held on Wednesday evening. Research conferences are held on every Friday 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 bedside 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.

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 and dermal papilla 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.

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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 two endowment departments: Department of Cartilage and Bone Regeneration (FUJI SOFT Inc.) and Department of Clinical Vascular Regeneration (Daiichi Sankyo Co., Ltd.) in Tissue Engineering Division. Each department has 1 associate professor, 1 assistant professor, and several graduate students respectively. 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 and prosthodontists. Special section for temporomandibular arthrosis is on Wednesday afternoon.

In the ward, we have approximately 400 new inpatients and surgical treatment is performed on approximately 300 cases per year. The main surgical treatments are chilooplasty and 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 patent.

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 by prosthodontists. 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) Multidisciplinary treatment of facial deformities in patients with cleft lip and palate or other congenital maxillofacial anomalies

- 2) Multidisciplinary treatment of dentomaxillofacial deformities, trauma and temporomandibular diseases
- 3) Multidisciplinary treatment of malignant tumors in head and neck region
- 4) Distraction technique of orofacial osteogenesis
- 5) Treatment for orofacial dysplasia with cleft lip and palate patients
- 6) Speech therapy for cleft lip and palate patients
- 7) Advancement therapy for congenital orofacial dysplasia
- 8) Evaluation of therapy for cleft lip and palate patients
- 9) Surgery, chemotherapy and irradiation therapy for malignant tumors
- 10) development of dental implant made of new materials
- 11) Advancement of orthognatic surgery for orofacial dysplasia
- 12) Evaluation of treatment for temporomandibular disorders
- 13) Evaluation of mastication function
- 14) Non-surgical treatment system for orofacial trauma
- 15) Reconstructive treatment utilizing custom-made artificial bone from our original technique

Basic and experimental research:

- 1) Contribution of periosteum to bone regeneration
- 2) Chondrogenic potential of the perichondrium
- 3) Bone regeneration using growth plate chondrocyte
- 4) Role of cell cycle factors in regulation of osteo-chondrocyte differentiation
- 5) Osteochondrogenic differentiation of bone marrow derived mesenchymal stem cells by spheroid culture
- 6) Periodontal tissue regeneration around dental implants
- 7) Reconstruction of bone and cartilage of oro-facial region using tissue engineering technique

Tissue engineering:

Clinical section

- 1) Clinical application of artificial bone that displace into bone
- 2) Implant type artificial bone generated from tissue engineered human chondrocyte

- 3) Therapy of regeneration blood vessel using AGHM- β FGF

Research section

- 1) Development of intelligent type of artificial bone invested with osteogenic differentiation factors
- 2) Development of tetra pod type micro artificial bone unit
- 3) Development of neo wound-care dressings
- 4) Three dimensional cell culture of autologous chondrocyte

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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 arthroscope 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 two associate professors, four lecturers, 13 associates, eight medical staff members, a visiting fellow, six 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, bedside learning and clinical clerkship programs to 5th year students and clinical lectures 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 10-day period of bed-side learning, students have opportunities to experience patient care and orthopaedic practice with residents and faculty members. We have developed an original text for the students to learn 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.

Clinical Clerkship provides 4 weeks of early 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 total 30 doctors-in-training (21 first-year doctors and 9 second-year doctors) completed our program during this fiscal year. Since the training period is short, they are encouraged to experience emergency cases as often as possible. A postgraduate seminar and a basic research conference are held weekly.

Including the postgraduate training, a ten-year course has been adopted with clinical and research training taking place either in the University of Tokyo Hospital or in our 50 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, and bone systemic disorders. A total of 36,891 patients visited the outpatient clinic in 2010.

The ward has approximately 55 to 65 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 Tuesday. Post- and preoperative case conferences are held on Monday evening, Tuesday morning and Thursday evening.

941 operations were performed in 2010. These include 101 cervical and thoracic spine surgeries (including 27 computer-assisted surgeries (CAS)), 85 lumbar spine surgeries, 27 scoliosis surgeries (including 26 CAS), 67 surgeries for rheumatoid arthritis patients, 107 hip surgeries, 202 knee surgeries (including 37 computer-assisted ACL reconstruction, 51 computer-assisted TKA), 6 shoulder surgeries, 130 hand surgeries, 8 limb lengthening and reconstruction surgeries using external fixators, 101 surgeries for bone and soft tissue tumor and 114 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 lumbar spine group developed a new posterior decompression technique which preserves the spinous processes and interspinous ligaments, and successfully uses it for lumbar spinal canal stenosis. Randomized clinical trials are now ongoing by this group.

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

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

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

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

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

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

Research activities

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

- 1) Molecular background of osteoarthritis using a mouse genomics approach
- 2) Signaling of differentiation and apoptosis of osteoclasts
- 3) Etiology of OPLL
- 4) Molecular background underlying the joint destruction by rheumatoid arthritis
- 5) Non-invasive evaluation of bone strength using a finite element method
- 6) In vivo bone formation by cytokines and its clinical application
- 7) Molecular mechanism of age-related bone and cartilage disorders
- 8) Molecular mechanism of glial cell differentiation
- 9) Ultrasonic evaluation of articular cartilage

In addition, four endowment departments take an active role in research activities in close collaboration with our Department. Two were established in the 22th 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 osteoarthritis 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, Sakata & Takai 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 vectors (polyion complex micelles).

We also take part in National Database of Rheumatic Diseases by iR-net in Japan (NinJa), a nationwide observational cohort database of rheumatic disease.

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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 speciality.

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, 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. Analysis with laser-speckle method of vascular flow in retina and iris
2. Clinical investigation of normal tension glaucoma
3. Drug effect on glaucoma
4. Screening method of glaucoma
5. Tissue engineering of the cornea
6. Clinical investigation of corneal shape
7. Novel culture system of corneal limbal epithelium and oral mucosal epithelium for ocular surface reconstruction
8. Analysis of Meibomian gland with Mibography
9. Clinical and basic research of excimer laser refractive surgery
10. Molecular analysis of retinal degenerative diseases
11. Color blindness and visual function
12. Electrophysiological analysis of the effect of drugs on the retina
13. Pathophysiology of age-related macular degeneration
14. Molecular analysis of retinal neovascularization
15. Immuno-hereditary analysis of Harada's disease and Bechet's disease
16. Immunosuppressive reagents on Bechet's disease
17. Pathophysiology and molecular mechanisms of diabetic retinopathy

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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. One assistant professor is abroad at present for basic and clinical research in the U.S.A. Moreover eight 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 bronchoesophagological surgery, and paranasal surgery and other minor surgery. Perioperative and postoperative problems are checked and discussed by each group, the professor's and associate professor's rounds. Approximately 800 operations are performed annually.

Cochlear implant surgery over 150 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, auditory brainstem response, and caloric test. Interview with patient is encouraged. They are questioned many aspects of clinical problems in seminars by professor and associate professor. During half and a week period, the students participate in surgery special clinics and practice of clinic examination such as otoscope, fiberscope auditory brainstem, caloric test and so on.

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 newborn 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.

Various clinical and basic research are conducted by staffs, residents, postgraduate doctors and senior 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. Eleven students have entered the graduate school by 2009, and eight of them were granted Ph.D.

Clinical activities

There is not enough doctors arranged for the department of rehabilitation medicine, and we cannot run own beds for rehabilitation patients at present. The professor serves as a director of Rehabilitation Center, the University of Tokyo Hospital. Both departments are united and engage in clinical practice. We have at present no charged ward, and treat about 1,000 new referrals annually from almost all the departments of the university hospital. We always take charge of about 250 patients corresponding about 25% of the whole number of inpatients. We also see 15 people per day at the outpatient rehabilitation setting. The numerical ratio of outpatient is being reduced in order to give priority to the clinical service corresponding to needs expansion of service to inpatients.

Teaching activities

We have provided several clinical curriculums on

rehabilitation medicine for 4th, 5th, and 6th year medical students since 1973. The systematic lecture series for 4th year medical students (M2) include the subjects on rehabilitation for disorders such as cerebrovascular disturbances, spinal cord injuries and spina bifida, neuromuscular diseases, bone and joint diseases, and cerebral palsy as well as on outline of rehabilitation, welfare system, and prostheses / orthoses . We have provided a clinical practice in small group, so-called bedside learning for 5th year students from Wednesday to Friday every other 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 clinical clerkship to our collaborating hospitals with specialized rehabilitation ward.

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

Eleven graduate school students entered by 2006 and six of them acquired a degree of Ph.D. and graduated.

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) Motion analysis of patients with joint disorders in the lower extremities
- 2) Motion analysis of motor development in children
- 3) Early detection, diagnosis, and progression prevention of musculoskeletal disorders in the elderly
- 4) Analysis of motion and energy expenditure in the activities of daily living in the physically disabled

- 5) Rehabilitation approaches for patients with spina bifida
- 6) Treatment and rehabilitation for patients with congenital limb deficiencies
- 7) Disabilities and handicaps in patients with skeletal dysplasias
- 8) Analysis of musculo-skeletal involvement in congenital insensitivity to pain
- 9) Rehabilitation of patients with hematogenic malignancies around the stem cell transplantation

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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. Our department has residents, chief residents besides the members above. We introduce the activities about Teaching, Research and Clinical work of our department.

Clinical activities

Our clinical activities can be divided into two areas; surgical anesthesia in the operating theater and a pain clinic.

Anesthesia service including pre and post-operative care is given every day for elective and emergency surgery. We provide general anesthesia for various kinds of surgeries including open heart surgery (adults and pediatrics) and heart / liver transplant, spinal/epidural anesthesia and monitored anesthetic care for electro-convulsion therapy. Recently, the

number of high risk or geriatric patients is increasing. In addition, more than 20% of the surgery among 8000 cases per year spends more than eight hours. A new operating theater opened in January 2007 and the demand for sufficient number of competent anesthesiologists is increasing.

Pain clinic services are provided for out-patients (including patients in the ward of the other department) on a daily basis in all areas of diseases accompanied with pain. We also provide preoperative anesthetic consult service for patients who have various medical complications. From April 2010 to April 2011, the number of ambulatory patients was about ten thousand; six hundred of those were newcomer patients. Currently we have three beds in the ward. Annually, we provide inpatient service for sixty patients in our ward as well as for seven hundred and twenty patients in other wards. Preoperative anesthetic consults were done for about twelve hundred patients last year.

Teaching activities

We give lectures for fourth year medical students and provide clinical education 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 bedside learning consists of three major contents: learning a practice of anesthetic management for patients undergoing surgeries, observing a practice of pain management for outpatients suffering from intractable pain, and interactive lectures on specific topics. During the practice of anesthetic management, we teach students how to evaluate patients in the peri-operative period. Through the practice of pain management, we teach students causes of intractable pain as well as procedures of nerve block. We schedule 5 lectures entitled “introduction to anesthesiology”, “airway management”, “central venous catheterization”, “spinal anesthesia” and “pain clinic”. These 5 lectures cover fundamental knowledge of basic procedures which medical students should acquire. Moreover, students can experience procedures of tracheal intubation, central venous catheterization and spinal anesthesia using simulators. Each student is required to submit a report of a case who underwent general anesthesia and the summary of anesthetics and cardiovascular drugs in peri-operative use. We discuss the contents of the reports and summaries with students at the end of bedside learning, 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) Dose-escalation of sublingual buprenorphine in patients with chronic pain
- 13) Analysis of electroencephalography during general anesthesia
- 14) Invention and evaluation of a new airway device
- 15) Clinical evaluation of neurological sequelae after cardiac surgery
- 16) Development and assessment of the system for treating waste anesthetic gases: against global warming
- 17) Effect of anesthetics on glucose metabolism *in vivo*
- 18) Role of new plasma substitutes on hemorrhagic shock

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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 Ophtho-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, high care unit (ICU2) of 24 beds, pediatric intensive care unit (PICU) of 6 beds and neonatal intensive care unit (NICU) of 6 beds.

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 the 2006, we had about 6,000 ambulance patients out of total 20,300 ER outpatients.

The new ER, four times the size of the present ER was built in November, 2006. The facility has 5 consultation rooms, 4 specialized consultation rooms for dentistry, ophthalmology, otorhinolaryngology and gynecology, 2 resuscitation bays, 1 operating room 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 2,700 ICU/CCU patients in the 2007. In 2007, the number of beds in ICU/CCU increased to 16 and the facility included the 24 beds for the high care ICU2.

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-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-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) from us. We are now proceeding with a drastic revision of in-hospital manual for disaster control, holding seminars on disaster medicine, and enforcing the disaster training. We have oxygen and medical suction equipment on the passageways in the new ER since 2006 fiscal year in case treating the large number of disaster patients.

Teaching activities

- 1) Six hours of lecture for the 2nd year medical student, the topics include the prehospital emergency care, the initial evaluation of emergency patients, disaster medicine, serious infections disease, and medical equipment. Four hours of simulation training of Basic Life Support.
- 2) One month of clinical clerkship and 1 week of bed-side training for the 3rd year. ACLS Basic course (ICLS) is held for the participants in the clinical clerkship program, and successful completion of this course will enable students to be ICLS certified.
- 3) 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. After learning a ACLS course, students experience the real practice of emergency medicine as fellow passengers in the ambulance and as 2.5-day trainees in affiliated hospitals' emergency centers.

In conformity with the guideline by Ministry of Health, Labour and Welfare, all residents learn and practice emergency medicine and primary care at every level, primary, secondary and tertiary. The residents are trained in the ACLS Basic (ICLS) 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.

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

As medical aspects of disaster management, we provide the residents with lectures based on MIMMS (Major Incident Medical Management and Support) program, triage training, and risk communication techniques using wireless network. In addition, we produce the seminar for nurses such as medical support in the big earthquake.

Research activities

The on-going researches include "the Vital Care Network System" which manages the great number of high-risk people continually, electrolyzed water, elucidation of peripheral neural regulation of heart, and brain resuscitation. In collaboration with Department of Pharmacy, Department of Clinical Laboratory Medicine, Department of Infectious Diseases, we focus on several clinical research on issues including intra-nuclear transcription of β -D-glucan in blood products.

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Health Sciences and Nursing

1. Health Sciences

Department of Health Sociology / Health Sociology and Health Education

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※For this department, this year's text is the same as that published last year.

Introduction and Organization

The Department of Health Sociology is one of the two departments which ex-Department of Health Sociology was divided into in 1997, when most departments in the University of Tokyo were reorganized into the Graduate School of the University of Tokyo. The department of Health Sociology is one of sixteen departments in the Graduate School of Health Sciences and Nursing. In 2007, Master Course only in the Division of Health Sciences was reorganized into the newly established school, the Graduate School of Public Health. The department where the master course students in the Department of Health Sociology get affiliated is named as the Department of Health Sociology and Health Education. The department consists of one Associate Professor (Chair of Health Sociology / Health Sociology and Health Education), 25 graduate students (8 master course students and 17 doctor course students) including 2 international students and 11 students qualified with nurse, and 5 research students. More than thirty visiting researchers are affiliated with the department.

Teaching activities

In Graduate Courses, School of Health Sciences and Nursing, Dr. Yamazaki, A. prof. and Head of Health Sociology, runs two seminars every year: Health

Sociology(I) in summer semester, and Health Sociology(II) in winter semester, with a lecturer, prof. Nakayama from St. Luca Nursing College.

The purpose of Health Sociology(I) is for students to obtain a basic understanding of the health sociological approach through a quick overview of major concepts, principles, and research in sociology of health and medicine.

Health Sociology(II) introduces students to basic methods and techniques in designing and conducting social research- in general, both quantitative and qualitative- in the health field. For these years, this seminar has been provided as Introduction to Multivariate Statistical Methods, and designed to learn the basic statistical methods such as factor analysis, analysis of variance/covariance, multiple regression analysis, multiple logistic regression analysis, and structural equation modeling.

For the graduate students and the other members in Dept. of Health Sociology, a workshop and a journal club are held every week. In the former, a student's research proposal or paper is to be reported and discussed. In the latter, a student is supposed to introduce an English article in the recent issue of an international refereed journal.

In our department in the fiscal 2009, 5 MC students submitted Master Thesis and gained Master's Degree. One DC student and one Ronpaku researcher submitted Doctoral Dissertation and got Doctor's Degree.

In Undergraduate Courses, School of Health Sciences and Nursing, our department is in charge of the following subjects as: Health Sociology (with a lecturer, Dr. Tamura), Social Welfare and Social Security (with two lecturers, Dr. Sakano from Okayama Prefectural University and Prof. Takagi from Keio University), Social Research Method Practice, Social and Human Relations, Graduation Thesis (many graduate students the last three subjects are shared with many graduate students in Dept. of Health Sociology), and the other two.

Research activities

Our department studies social and psychological factors related to health problems and health care systems, through developing and applying theories, concepts and methods, which have been developed in sociology, psychology, and social and behavioral sciences.

We have been conducting the following 7 research projects on going.

1. Studies on Antonovsky's Salutogenesis and Sense of Coherence (SOC) Concept

We have introduced Antonovsky's Salutogenesis and its core concept 'Sense of Coherence (SOC)' to Japanese fields of health and stress. The objective of this project is to develop and apply Japanese version Antonovsky's SOC scale to examine SOC and correlates among different population, people with chronic illness/disability, and so on.

2. Study on People with Medically Induced HIV

Nearly 1,500 hemophilia patients were infected with HIV through blood products in the mid 1980's in Japan, and so far more than five hundred patients have died of AIDS and others. They are suffering not only from health damage but also various types of stigma and discrimination. In this project, several research studies are being conducted in order to explore the problems of their lives, and to suggest the needed social supports

3. Studies on Social Differences and Inequalities in Health

This project is designed to explore evidence about socio-economic differences in health, especially

among the middle-aged, in Japan. Another purpose of this project is to consider possible explanations for these differences and the implications for policy.

4. Studies on Changing Professional-Patient Relationship and Patient Autonomy

The aim of this project is to examine the current situation of professional-patient relationship and patient autonomy in Japan, and to derive new theories. Both empirical and theoretical studies have been conducted from various perspectives.

5. Studies on "Way of Working and Living" and Fatigue/Stress of Working People

Recently Japanese industrial society has been subjected to the never-experienced structural changes. The aims of this project are to explore the effects of these changes on "ways of working and living", work-family balance and fatigue/stress of working people, and to clarify the mechanism of the effects.

6. Studies on Characteristics of the Physical and Psychological Distresses in Human Service Work

Human service work is spread over the many fields including medicine, nursing and caring. The aims of this project is to examine the characteristics of the psychological and physical distress of human service workers and their related factors.

7. Studies on the Onset of Pneumoconiosis among Tunnel Construction Workers

In Japan, many tunnel construction workers suffered from the onset of severe pneumoconiosis in 1970's. It is still continuing in 1990's. The purpose of this research project is to reveal the process and the related factors on the onset of pneumoconiosis in recent years.

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Department of Mental Health

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Introduction and Organization

The department was firstly established as Department of Fourth Clinical Medical Nursing in School of Health Care and Nursing in 1957. When the School of Health Care and Nursing was reorganized as the School of Health Sciences in 1965, the department was renamed Department of Mental Health. In 1992, as School of Health Sciences became The School of Health Science and Nursing, Department of Mental Health became Department of Mental Health and Psychiatric Nursing. As the result of the shift to the chair system of the Graduate School of Medicine in 1996, two departments were established, Department of Mental Health and Department of Psychiatric Nursing. Faculty, staff, and students of two departments have been working cooperatively ever since.

The department currently has faculty members introduced above, part-time lecturers, a technical specialist, visiting research fellows, 6 doctoral course students, 3 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 leading practitioners and clinical researchers in the field. The other is to conduct clinical research in the fields of mental health.

All of the activities of the department are

conducted in collaboration with staff members in the department of psychiatric nursing.

Teaching activities

The department is responsible for giving lectures on mental health; mental disorders; clinical psychology; and psychometry and behavior evaluation to undergraduate students. Other than lectures, the department provides students opportunities to practice mental health activities in several relevant mental health facilities.

The department provides courses on mental health I and II, featuring research methodology of epidemiology in mental health and occupational mental health, respectively, in the fiscal year of 2010. 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, including presentation of a research plan by each graduate student and relevant discussion, presentation of literature review, and lectures by guest speakers.

Research activities

The department conducts research on mental health and psychosocial stress 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, and work-life balance) are also actively investigated. Furthermore, research in the department includes various other topics, such as psychiatric rehabilitation, clinical psychology, psychotherapy, child and adolescent psychiatry; and developmental disorders. 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 changed the name from “Epidemiology” in 1992 and has responsibility for providing educational courses on epidemiology and biostatistics to undergraduate students as well as graduate ones. As compared to the situation in the United States, the education of biostatistics and methodological aspects of epidemiology is poor in Japanese universities and graduate schools, although the necessity for collaboration with biostatisticians in clinical research (especially clinical trials) is recently being to be claimed by clinical researchers and pharmaceutical industry. One mission of our educational courses is to provide detailed knowledge and experiences in biostatistics/ epidemiology to students who are expected to take part in clinical/epidemiological research as experts and the other mission is to provide basic principles of biostatistics/epidemiology to students who will work in many health-related fields including nursing. Our main research project is the

development of methodology for clinical/epidemiological research and it requires keeping touch with real clinical/epidemiological problems. For these purposes and research coordination, a non-profit organization titled ‘The Japan Clinical Research Support Unit’ was established by the faculty members in 2001, and the organization is providing research support in design, data management and statistical analysis in many projects inside/outside the university.

The faculty of the department provided lectures in a series of educational courses organized by ‘The Clinical Bioinformatics Research Unit’ in 2002-2007.

Teaching activities

1. Undergraduate courses

- 1) Epidemiology and Biostatistics (2 credits)
- 2) Applied Mathematics (2 credits)
- 3) Statistical Methods and Information Processing (2 credits, practice)
- 4) Design and Analysis of Epidemiological Research (2+1 credits, 1 practice)

- 5) Medical Data analysis (2 credits)
- 6) Biostatistics (2 credits; for the School of Medicine)
2. Graduate courses
 - 1) Biostatistics (4 credits)
 - 2) Epidemiology and Preventive Health Sciences (4 credits)
 - 3) Introduction to Medical Statistics (2 credits; for the School of Medicine)
3. School of public health
 - 1) Statistical Analysis of Medical Research (2 credits)
 - 2) Practice of Biostatistics (2 credits)
 - 3) Design of medical Research (2 credits)

Research activities

- 1) Biostatistics and Theoretical Epidemiology
 - Analysis of longitudinal missing /incomplete data
 - Analysis of multiple events data
 - Analysis of QOL data
 - Causal analysis
 - Analysis of micro/macro array data
 - Meta analysis of epidemiological studies
- 2) Methodology and Information Systems for Clinical Trials
 - Design of clinical trials
 - Data management of large-scale clinical trials
- 3) Pharmacoepidemiology
- 4) Coordination of collaborative epidemiological/clinical research
 - Japan Arteriosclerosis Longitudinal Study
 - Japan Diabetes Collaborative Study
- 5) Consultation Works with Corporate Sponsored Research Program 'Clinical Data Management'

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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, an associate professor, a lecturer, an associate, and a technical specialist. All five members, six undergraduate lecturers and eight graduate

lecturers from other organizations, and ten visiting researchers contribute to department teaching and research activities.

Department graduate students included four master program students and three 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. Eight bachelor theses, twelve master theses, and six doctoral dissertations were completed between April 2004 and March 2011. Our departments' staff members are also responsible for the following undergraduate and graduate courses.

Undergraduate Courses

Required courses

- 1) Health Administration (2 credits, lecture)
- 2) Biomedical Ethics (2 credits, lecture)
- 3) Occupational Health and Law (1 credit, lecture)

Elective courses

- 4) Health & Education (2 credits, lecture)
- 5) Health Care & Welfare I & II (2 credits, lecture)
- 6) Field Work for Health Administration (2 credits, practicum)
- 7) Health Promotion Sciences (1 credit, lecture)
- 8) Health Policy & Administration (2 credits, lecture)

Graduate Courses

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

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. The main foci in the graduate courses of Health Promotion Sciences are the assessment and design of the health promotion projects in the community and at the work place, and

the development of preventive health strategies and health promotion related to life-style related disease.

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

Specific research topics include:

- 1) Study of methods for promoting social consensus on topics related to advanced medical technology
- 2) Study of the function and responsibilities of ethics committees in Japan
- 3) Acceptability of advance directives in Japanese society
- 4) Development of evaluative methods for biomedical 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 making health policy proposals concerning health promotion in the community and work place through experimental and survey research. The main research fields are health behavior and life-style related disease. The main focus of health behaviors are physical activity including exercise, diet and nutrition, and obesity. Our department is providing lectures and practical training with the aim of helping students to understand the method of planning, implementation, and evaluation of the health promotion programs in the community and the work place.

Specific research topics include:

- 1) Development of effective health promotion programs
- 2) Assessment of and supporting methods for health behavior and the impact on health status
- 3) Short and long term effects of behavior change
- 4) Influence of behavior change on medical costs and cost effectiveness analysis
- 5) Determinants in the social and physical environment on the adherence to behavior change
- 6) Survey of health promotion resources in the community and at the work place
- 7) The development of a physical activity questionnaire for the Japanese
- 8) Multiple risk factors and health behavior
- 9) Dietary patterns among overweight men and women

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Health Sciences and Nursing

2. Preventive and Administrative Nursing

Department of Nursing Administration / Advanced Clinical Nursing

Professor

Katsuya Kanda, Ph.D., R.N.

Assistant Professor

Mami Onishi, M.S.N., R.N., Ayako Nagata, M.A., R.N., Satoko Nagai, M.S.N., R.N.

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Introduction and Organization

Nursing Administration department provides broad opportunities to learn about societal issues related to; 1) nursing administration, nursing policy, nursing education, nursing ethics, and 2) safety and quality issues in nursing.

Advanced Clinical Nursing department provides; 1) critical analysis and synthesis of conceptual frameworks, nursing theories and models for advanced practice, and 2) generation and utilization of evidence related to practice, understanding of clients, and fundamental skills.

As we expect much of the graduates to develop their professional carriers in various settings, we are constantly exploring new issues to make students be able to take wide and long viewpoints.

Teaching activities

Graduate courses

Nursing Administration 1 (2 credits, Lectures)

Prof. Kanda and Affiliates

Exploration of political and administrative functional role in nursing. The course offers critical analysis of theories in nursing administration related to quality assurance/ improvement and cost- effective/efficient care delivery systems. Discussions include concepts

and structures in organization, decision/policy making process, and application of management theory and nursing process to nursing administration. Theory and practice in nursing education is also explored.

Nursing Administration 2 (2 credits, Lectures)

Prof. Kanda and Affiliates

Studies on application of management theory to nursing administration. Focuses are on; 1) issues in nursing management such as budgetary management, nursing informatics, patient classification systems, staffing, and quality improvement, and 2) issues in staff management such as staff development and continuing education. Students will learn concepts and skills essential to solving economic issues in health care and nursing to meet professional demands in the complexity of health care systems.

Advanced Clinical Nursing 1 (2 credits, Lectures)

Prof. Kanda and Affiliates

An overview on models, theories and research in nursing. Focuses are on; 1) conceptual frameworks of clients' potential and actual physiological and psychosocial responses to health problems, 2) health assessment skills in nursing practice, 3) measurement of clients' health and nursing intervention outcome. Students will establish their own theoretical knowledge and practical skills essential to advanced clinical nursing.

Advanced Clinical Nursing 2 (2 credits, Lectures and practicum)

Prof. Kanda and Affiliates

This course explores issues related to advanced clinical practice, research, and education with an emphasis on specific theoretical perspectives, methodologies, practice and economic implications.

Undergraduate Courses

First Aid & CPR (1 credit, Lectures & practicum)

Prof. Kanda and Affiliates

Students will understand the emergency medical system and learn how to act in emergency situations. The practicum includes following subjects; 1) observation and measurement of vital signs, 2) first aid to the victim with bleeding, intoxication, or burn, 3) how to carry an injured person, and 4) CPR (cardiopulmonary resuscitation).

Fundamental Nursing 1 (2 credits, Lectures)

Prof. Kanda and Affiliates

This course offers fundamental knowledge of nursing, such as history and theory in nursing, concepts of professional nursing practice, nursing service and care delivery systems, nursing administration, and nursing education. Discussions include contemporary challenging issues and future strategies in nursing.

Fundamental Nursing 2 (2 credits, Lectures)

Prof. Kanda and Affiliates

This course offers fundamentals in understanding interpersonal relationships and assessing clients' health. Students will learn; 1) theory and practice in communication, 2) knowledge necessary for identifying health problems and care priorities, 3) skills essential to health assessment, 4) nursing process and nursing diagnosis, and 5) current ethical issues in nursing and health.

Fundamental Nursing 3

(4 credits, Lectures and laboratory practicum)

Prof. Kanda and Affiliates

This course provides theory and practice of fundamental nursing skills, which are essential to providing clients with; 1) safe and effective care environment, 2) physiological and psychosocial integrity, and 3) health promotion and maintenance.

Clinical Practicum in Fundamental Nursing (2 credits, practicum)

Prof. Kanda, Staffs and Affiliates

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

Nursing Administration (1 credit, Lectures)

Prof. Kanda and Affiliates

This course prepares students for nurse administrators/managers of all types of health care settings such as institutions, organizations, community and politics. Students will learn fundamental theory and practice in nursing administration/ management through analyzing current issues in health care and nursing.

Nursing Administration Practicum (1 credit, practicum)

Prof. Kanda and Staffs

Students have administrative/ management practicum in units or divisions in hospitals. Students will learn care delivery systems such as staffing and patient classification systems, nursing informatics, and budgetary issues including cost effectiveness and quality improvement.

Research activities

Nursing research starts with an approach to address a variety of complex problems related to health experience of human beings' daily life. Philosophical orientations and research methodologies may include natural scientific (or biomedical, quantitative, statistical) approaches, or social and human scientific (or narrative, qualitative) approaches, or combination of both approaches.

Issues of Nursing Administration

Critical analysis and international comparative study of administrative, socioeconomic and political issues in contemporary nursing. Focuses are on; 1) patient classification systems and nursing care delivery systems, 2) cost- effectiveness of nursing services, 3) nursing case management, and 4) nursing policy and strategies to meet the professional demands.

Quality Improvement, Safety Issues, and Risk Management in Nursing

This work examines; 1) quality of nursing care, 2) outcome management for nursing practice, 3) risk management in acute care settings, 4) occupational safety and health of health care workers, and 5) infection control.

Physiological and Psychological Human Responses to Stimulus

This area of study aims at exploring the nature, or determining various effects of physiological and psychological stimulus to participants' physiological bio-information and psychological measurements. Research scenarios include; 1) patient' daily activities, 2) caregivers' workload and sleep deprivations, or 3) nurses focus of attention, eye movement, and electroencephalography activities. Data collections take place through field studies or laboratory/ experimental settings.

Nursing Assessment and Intervention

Exploration of structure of existing discipline and development of new nursing theories in clinical practice. Emphases are on; 1) explorations of structure of nursing theories and models in nursing, 2) development of clinical and scholarly knowledge for the identification of health problems and assessment of care priorities, and 3) testing hypotheses effective for nursing interventions

Studies of Nursing Education

Exploration of nursing education systems and functional roles of professional nurses in various settings in advanced countries and developing countries as well. Higher education for the advanced practice nurses in Japan is also explored.

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Department of Family Nursing

Associate Professor

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Lecturer

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Introduction and Organization

This department was established in 1992. The Japanese Association for Research in Family Nursing was founded by this department in 1994. Currently, it has four faculty members: an associate professor, a lecturer, and two research associates. Also it has 11 doctoral students, 10 master's course students, and 17 visiting scholars.

Education

1. Graduate Courses, School of Health Sciences and Nursing
 - Advanced Family Nursing I
 - Advanced Family Nursing II
 - Laboratory and/or Field Work on Family Nursing
 - Practice in Translational Research Nursing
 - Advanced Nursing Consultation
2. Undergraduate Courses, School of Integrated Health Sciences
 - Family Nursing
 - Pathophysiologic Immunology
3. Undergraduate Courses of Nursing, School of Integrated Health Sciences
 - Pediatric Nursing
 - Clinical Practicum in Pediatric Nursing
4. Undergraduate Courses of Midwifery, School of

Integrated Health Sciences

Midwifery III

Clinical Practicum in Midwifery

Research

The topics of our current research projects are as follows:

1. Postnatal depression and difficulties in childrearing.
2. Prevention of child abuse and neglect.
3. Development of Pediatric QOL Inventory for child with chronic illness and their parents.
4. Late effect of treatment and posttraumatic stress disorder in children with cancer.
5. The roles and expertise of the nursing staffs in daycare centers.
6. Primary caregivers' burden of the severely disabled children and the utilization of the respite care.
7. Care for dying patients and their families (QOL, family function).
8. Development of Japanese version of Families' Importance in Nursing Care – Nurses' Attitudes.

Publications

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Department of Community Health Nursing / Public Health Nursing

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. At present, there are four faculty members introduced above and 24 graduate course students (14 in master course, 10 in doctoral course) in the department. Also, we accept many visiting researchers from other colleges and institutions.

Teaching activities

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

1) Community Health Nursing (4 credits, lectures)

Community health nursing is a study to develop the caring techniques and the method to evaluate the effectiveness of care not only for a person but also for a whole community. This class is to study, the concepts and functions of community health nursing, developing process of community health nursing, community assessment and

activities of community health nurses.

2) 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.

3) Health Guidance (2 credits, lectures)

This class is to study the methodology and practice of health guidance, which is the supporting technique to promote health of the people living in the community.

4) Community Health Nursing Practice (2 credits, practice)

This program is intended to understand the system of health promotion and prevention by attending the actual community health nursing activities at health center. Students are expected to realize the principle and the common technique of community health nursing activities by observing the activities of public health nurses.

5) Home Health Nursing Practice (1 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.

6) Health Assistance Practice I•II (2 credits, practice)

In this program, students will comprehend multilaterally how characteristics of the residents, health resources and environment of the community effects health and discuss on the health matters of the overall community. In addition, students will visit various working sites for nurses to deepen their knowledge of multiple health related resources, and learn the actual skills of health guidance towards individuals/ families/ groups through experience.

2. Graduate program, in the Graduate School of Health Sciences and Nursing

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 is to study the research issues on home care and methodology of qualitative research for community health nursing.

3) Advanced Public Health Nursing I (2 credits)

This program is to study the theoretical concept of community health nursing, assessment of the community, problem finding, prioritization procedure, and planning, operation and evaluation of countermeasures needed in advanced community health nursing practice using the textbook for master course students in western countries.

4) Advanced Public Health Nursing II (2 credits)

This program is to understand policymaking of national and local government, method to operate and evaluate the systems, and approach to policy development as public health nurses through lectures by experts of public policy and social welfare.

5) Advanced Community Health Nursing Seminar I,

II and Practice I, II

Especially in Public Health Nursing course, practices for sequential home visiting, community assessment / activity, and community health nursing management are given.

In addition to these programs, we have department meeting (journal reading and research introduction) on every Tuesday and monthly seminar on every 3rd Friday.

Research activities

Our research focuses on the development and evaluation of health care programs, establishment of community health care systems, and standardization of skills of public health nurses, in response to the health care needs of individuals, families, aggregates and the communities. We are conducting researches on Grant-in-Aid for Scientific Research of Ministry of Education, Culture, Sports, Science and Technology, Health Science research Grants of Ministry of Health, Labour and Welfare, and grants from some foundations.

Research projects which are undergoing in our department are listed below.

1. Developing community health nursing activity model of public health nurse

In collaboration with community health organizations, we intend to develop the evaluation method of community health nursing activities according to the natural characteristics of each community by public health nurses, and develop methodology to provide subsequent nursing efficiently. Pioneering community health nursing or health activities by public health nurses are chosen, their degree of performance and current situation are evaluated in several small areas, and the way to develop the activity according to each areal feature is discussed.

2. Skills of public health nurses

We aim to clarify and standardize the skills of public health nurses especially focusing on “personal support”, “policy making” and “support towards tuberculosis patients”. In concrete, we are analyzing the interviews by experienced PHNs and extract their

support skills, compare their practice with existing theory, conduct surveys, and explore elements related to support. Also, we are developing health guidance solution for individuals/groups/community by literature review and field study.

3. Establishment and evaluation of community health care systems

The project has been designed to reform service systems and currently being evaluated. The around-the-clock in-home care system and discharge planning system are examples of these researches which are now being conducted. Furthermore, we are conducting the research to promote community organization and interorganizational network.

Especially about the around-the-clock in-home care system, through the model project at visiting nurse services stations, we clarify the effects of the services and the methods to establish the system. Also we are developing method of measuring effect of home-visit nursing with accompany of care staff and efficiency of visiting nurse service stations.

4. Discharge planning

Discharge planning is an interdisciplinary process that should be available to aid patients and their families in developing a feasible plan for the next place of care, and there is an increasing demand for it. We are trying to standardize discharge planning activities, to develop the outcome indicator of discharge planning, and to produce the educational program of discharge planning for ward nurse. We are conducting research about discharge planning system, developing the guidelines for multisectoral and interagency cooperation among nurses and the method for evaluation of the capacity of discharge planning nurses by investigation of actual situation.

5. Support for families with babies and children

We are conducting researches covering two fields, community health and occupational health. The former researches are aimed to prevent and reduce anxieties of mothers and the latter is to support mothers and fathers balance their work with child-care. Our interest is specially on health concern and action in child raising families, mothers' difficulty of child-rearing and their children's behavioral

characteristics. Also, the network for childrearing was investigated to prevent child abuse.

6. Support for people with diseases or disabilities

We are making researches for people with diseases or disabilities to improve their QOL.

The research themes in 2009 are 1) Condition, reason of admission and succession of residents at geriatric medical care facility for the elderly, 2) Psychological experience of the mother who delivered to Down syndrome child, 3) Acceptance to diseases and experiences in hospitalization for tuberculosis patients, 4) The characteristics of patients with delayed hospital visit for tuberculosis diagnosis and 5) The factors relating to the time of PEG among patients with ALS.

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Health Sciences and Nursing

3. Clinical Nursing

Department of Adult Nursing / Palliative Care Nursing

Professor

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Introduction and Organization

The Department of Adult Nursing / Palliative Care Nursing originated as the “Department of Adult Health” in the School of Health Sciences (1965-1992), later becoming the “Department of Adult Health and Nursing” in the School of Health Sciences & Nursing (1992-).

From 1995 to 1997, the Graduate School of Medicine shifted to a Graduate School chair system, and our two newest departments were established. The members of these two departments cooperate in educational and research projects.

Our department also takes charge of the Certified Nurse Specialist course newly established in 2008.

Education

In undergraduate courses, our departments have the chair of Lecturer and school- and hospital-based practicums in adult nursing. In addition, our departments have the educational responsibility of teaching students about “disease in adult populations I and II”, which is a basic discipline for adult nursing.

In graduate courses, the two departments cooperate in education and research. In particular, during the first term of the doctoral course (master’s course), in which students learn basic research skills, the focus is on the effective and efficient management of both fields.

Graduate students prepare their dissertations by developing research question from their own scientific interests or by participating in departmental projects. Since we consider that the process itself is a part of the educational training of researchers, we focus our energy on seminars for developing master’s and doctoral theses.

Research

Our department conducts research on adult nursing from various points of view. One such perspective focuses on the course of a disease, in which not only the periods of recovery and terminal treatment but also the upstream preventive steps, before disease onset, are assessed with the chronic phase in the center; therefore, such nursing comprises an extremely wide range of periods of practice. We have been

conducting studies which are expected to allow us to understand the state of individuals who require nursing in those periods, and investigations on effective and efficient nursing care for such individuals.

Another theme regarding nursing systems is how care should be provided for individuals in the most appropriate ways. We have been investigating how nursing should be provided, and the continuity of nursing care in various settings, such as outpatient clinics, at home, and in palliative care facilities, by focusing on individuals before disease onset, in the chronic phase, in the recovery period, and in the terminal period. We consider that it is essential to eliminate and/or improve the difficulties nurses in these settings must confront, since they are associated with the improvement of care; therefore, such issues have also been investigated.

Furthermore, one of our research themes is the development of evaluation measures and scales, which are required in such studies.

Herein, we describe our current research areas. You may refer to our homepage for more information, such as the details of our research achievements, and the acquisition of research funds. The resources that have been developed in our research, such as evaluation scales, are freely available to the public via our homepage.

1) Nursing for Patients with Chronic Illnesses

It is necessary for individuals with chronic illnesses to conduct self-management for symptom control in their daily lives. Nursing has the important role of supporting patients to maintain their lifestyle by continuing self-management in their daily life.

We have developed various instruments for measuring the difficulties that patients with chronic illnesses experience in their daily lives, and have described actual situations of difficulties using these instruments. Furthermore, we have conducted a study regarding support for controlling symptoms in order to reduce such difficulties.

The summaries of these studies, including some theses in preparation for publication, are briefly described below.

Diabetes (DM): We have developed preventive strategies for adult offspring of diabetes patients and

confirmed its possible effectiveness and feasibility. We take this approach into public health setting; controlled trial of computer-based lifestyle intervention combined with genetic counseling has been started at medical checkup institution.

Inflammatory bowel disease (IBD) : To study the issues associated with providing information to Japanese IBD patients, we conducted two studies. The aim of the first study was to describe the contents of brochures given to patients with IBD in Japanese hospitals. These brochures were compared to those used in Western countries. The existing situation for providing information in Japanese hospitals was unsatisfactory. Furthermore, we revealed the characteristics of information provided in Japanese hospitals. As a result of these characteristics, second study was conducted to investigate medication adherence and difficulties in taking their medicine. We suggest that it is important to provide reasonable and specific information to improve their adherence.

2) Nursing for Recipients and Donors in Advanced Medicine (organ transplantation)

In a transplantation therapy in advanced medicine, both recipients and donors experience various difficulties, which have not been observed in conventional medicine. Reduction of such difficulties is also important in nursing.

Generally, self-management behavior such as maintenance of immunosuppressive medication adherence is essential for patients after transplantation to achieve long-term graft survival. We have investigated the implementation status of recommended self-management behaviors for kidney-transplant recipients and its association with their post kidney-transplantation period.

We have also contributed to establish donor coordination system in the hematopoietic stem cell transplantation (HSCT) thorough the project which develops adult donor coordination guideline about related HSCT.

3) Nursing Care System for Outpatients

Recently, the role of nursing in hospital outpatient care and home care has changed dramatically due to the decrease in the duration of hospitalization, the increase of chronic diseases, and the increase of the

elderly population. In the field of adult nursing, we focus on consultation and guidance in outpatient care in order to support self-management of chronic diseases by nurses who are specialized in each disease categories. We had performed nation-wide surveys which aim to clarify the effectiveness of nurse specialist assignment, and conducted educational activities regarding the promotion of nursing activity in outpatient care.

4) Genetic Counseling

Genetic counseling for patient and their family who have concerns about hereditary disease is an important and unique research field for our department. Current researches mainly focused on public health genomics, disease management in patients with familial cancer, and establishment of medical system about genetic test.

5) Home Care for cancer patients

A large number of patients wish to receive end-stage care at home; however, many difficulties are involved in the realization of such requests. Thus, it is one of the most important problems in palliative care in Japan.

Visiting-home nursing has an important role in palliative care at home. So we tried to facilitate the visiting-home nursing practice by identifying barriers for providing that in clinical setting. We also developed screening tool for the needs to visiting-home nursing.

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Department of Midwifery and Women's Health

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Introduction and Organization

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

Currently, it has 4 faculty members introduced above and 10 part-time lecturers, 4 graduate students (1 in master course, 3 in doctoral course) and 2 visiting researchers.

Teaching activities

We have graduate and undergraduate courses for midwifery and maternal care, and women's health.

1. Graduate Courses, School of Health Sciences and Nursing
 - 1) Advanced Midwifery and Women's Health 1 (2 credits, lectures)
 - 2) Advanced Midwifery and Women's Health 2 (2 credits, lectures)
2. Undergraduate Courses of Nursing, School of Health Sciences and Nursing
 - 1) Maternity Care and Nursing (2 credits, lectures)
 - 2) Maternity Care and Nursing Practice

(2 credits, practice)

3. Undergraduate Advanced Courses for Midwifery, School of Health Sciences and Nursing
 - 1) Midwifery 1 (1 credit, lectures)
 - 2) Midwifery 2 (1 credit, lectures)
 - 3) Midwifery 4 (3 credits, lectures)
 - 4) Administration for Midwifery (1 credit, lectures)
 - 5) Clinical Practice of Midwifery 1 (1 credit, practice)
 - 6) Clinical Practice of Midwifery 2 (7 credits, practice)

Research activities

Our research activities are focus on maternal and child health with emphasis on the promotion of women's health and their quality of life at every stage throughout the life span.

We conduct the following research projects:

1. Collecting evidence for health guidance during pregnancy.
 - 1) Adequate maternal nutrition and weight management.

Maternal body composition, lipid metabolic biomarkers and nutritional intake are examined to optimize weight control and a healthy lifestyle during pregnancy to prevent a low birth weight. Based on our investigations on the optimal maternal nutritional status and gestational weight gain, we propose health guidance which can help pregnant women to lower their risk of pregnancy complications and their babies' risk of adverse birth outcomes.

2) Lifestyle factors and oxidative stress during pregnancy.

The study aims to assess the potential relationships between lifestyle factors and some oxidative stress markers during pregnancy and to establish optimal oxidative stress markers for predicting healthy lifestyle for pregnant women.

3) Plasma total homocysteine (tHcy) during pregnancy and the infant's birth weight.

There are conflicting evidences that shows elevated tHcy contribute as a risk factor for intrauterine growth retardation.

This study aims to determine whether tHcy is a risk factor for the fetal growth.

4) Evaluation of a dietary assessment tool for Japanese pregnant women.

Validity, reproducibility and factors related to the under- or over-reporting of a self-administered diet history questionnaire (DHQ/BDHQ) among Japanese pregnant women are studied.

2. Development of accurate predictors of postpartum hemorrhage.

Possible associations of multiple biomarkers with uterine smooth muscle contraction or relaxation (13, 14-dihydro-keto- prostaglandin F_{2α} and Nitric oxide metabolites) and postpartum hemorrhage are studied.

3. Development of self body management support system after delivery

1) Postpartum stress urinary incontinence and the transverses abdominis /pelvic floor muscles.

We conduct functional evaluation of postpartum local muscles using ultrasonographic method.

These techniques are developed to establish the relationship between the pelvic floor or

abdominal muscles and urinary incontinence among women across lifespan.

2) Development of the preventive and restorative program of pelvic floor muscle hypergasia.

The use of ultrasonographic method as a biofeedback tool for body management is evaluated.

3) Anal sphincter defects after delivery.

Prevalence and risk factors of anal sphincter defects among postpartum women are determined by using three-dimensional transperineal ultrasound.

4) Promotion of women's health care after delivery.

The relationship between maternal body composition and lifestyle factors including breast feeding among postpartum women are studied.

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Department of Psychiatric Nursing

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Introduction and Organization

Our department was firstly established as Department of Fourth Clinical Medical Nursing in School of Health Care and Nursing in 1957. When the School of Health Care and Nursing was reorganized as the School of Health Sciences in 1965, the department was renamed Department of Mental Health. In 1992, as School of Health Sciences became The School of Health Science and Nursing, Department of Mental Health became Department of Mental Health and Psychiatric Nursing. As the result of the shift to the chair system of the Graduate School of Medicine in 1996, two departments were established, Department of Mental Health and Department of Psychiatric Nursing. Faculty, staff, and students of two departments have been working cooperatively ever since.

Our department currently has two faculty members introduced above, part-time lecturers, visiting research fellows, 6 doctoral course students, 3 master course students, and research associates.

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

All 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.

The following is a master's thesis theme from our department in 2010.

- "Reliability and validity of the Japanese version of the Drug and Drug Problems Perception Questionnaire for nurses."

The following are PhD thesis themes from our department in 2010.

- “Study of parental difficulties in families with Hikikomori syndrome children (Social withdrawal).”
- “Analysis of home nursing care for people who have schizophrenia.”
- “Relationship between manager communication behaviors and mental health among hospital nurses in Japan.”

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 for people with mental health difficulties; community support system for the people with mental health needs; peer support; stigma; social inclusion; issues of caregiver burden in family caregivers; behavioral and psychological symptoms of dementia; patient satisfaction with psychiatric services; and practice and evaluation of home visiting psychiatric nursing. We are conducting studies in collaboration with researchers in other institutions and universities.

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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 project lecturer, 1 lecturer, 1 research associate, 1 project research associate, and 7 part-time lecturers for undergraduate course (2) and for graduate course (5). The student body consists of 10 doctoral course students, 11 master course students and 1 undergraduate student. 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) Gerontological Nursing (3-4th 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 2010 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) Social, health and medical policies for a healthy life of the elderly
- e) Drug induced geriatric syndrome
- f) Geriatric syndrome and nursing (gait disorder, malnutrition, infection, dementia and pressure ulcer)
- g) Future perspectives of gerontological nursing

The aim of the 4th year course is to promote understanding of the ailments and conditions required

to provide proper care to the elderly. The main themes in the 2010 contents were as follows;

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

The above lectures were developed under the cooperation by the Department of Geriatric Medicine at The University of Tokyo Hospital.

2) Clinical Practice in Gerontological Nursing (4th yr/ 3 credits)

The aim of this practicum is to learn present situation of gerontological nursing through practicing in the long-term care facility. This program in 2010 was supported by the long-term care facility owned by Medical Corporation Tatsuoka.

3) Bachelor's thesis

The following was the research theme in 2010;
"Impaired AQP3 expression in epithelialization of skin wound healing in diabetes"

2. Graduate course

1) Gerontological Nursing I (Summer course/ 2 credits)

2) Gerontological Nursing II (Winter course/ 2 credits)

This program focuses on studying the recent research trends and problems related to the elderly.

The main theme of Gerontological Nursing I in 2010 was geriatric syndrome. The students were instructed to learn the research trends of geriatric syndrome through critical reading of recent papers. Future perspectives of gerontological nursing were also discussed. Geriatric syndromes such as fall, delirium, depression, dysphagia, malnutrition, urination disorders, pressure ulcers and dementia were included in this program.

Gerontological Nursing II provided lectures regarding

the recent topics around gerontological medicine and nursing from the broad viewpoints including biological, individual and social aspects by the part-time lecturers, specialists of each research field. The aim of this course was to obtain scientific ways of thinking for gerontological considerations of the future Japanese community. The main themes in 2010 were as follows;

- a) Biochemical fundamentals required for nutritional management
- b) Physical and mental approach of terminal care based on nutrition and metabolism
- c) Relationship between psycho-social factors and health outcomes in the community based elderly
- d) The present status and problems in the nursing education and preventive training against natural disasters in the center hospital of disaster medicine
- e) Support for younger dementia patients and their families
- f) Development and evaluation of the high-risk preventive care approach program for the elderly with mild cognitive impairment (MCI)
- g) Quality evaluation of gerontological nursing

3) Wound Care Management I (Summer course/ 2 credits)

4) Wound Care Management II (Winter course/ 2 credits)

The main theme of Wound Care Management I in 2010 was the critical reading and related discussion of the textbook "Bioengineering Research of Chronic Wounds" (Amit Gefen et al. eds. Springer, 2009). This textbook is a multi-disciplinary omnibus of recent researches in this field including a chapter from our laboratory, offering the newest information of prediction, prevention, diagnosis and treatment of chronic wounds from the standpoint of bio-cellular engineering.

Wound Care Management II in 2010 was a series of lectures entitled "Cutting Edge of Wound management: from basic researches to clinical applications." The lecturers with advanced experiences in this field were invited from various institutions to give lectures as follows.

- a) Inflammaging: a new perspective of the aging and its evolution.

- b) Intestinal stoma and its complication
- c) Application of regenerative medicine to wound management
- d) Cell biology in dermatology (the special lecture held jointly with Department of Advanced Skin Care)
- e) Aging and senescence of the skin
- f) Breast cancer and the fungating wounds

5) Master's thesis

The followings were research themes in 2010;

“Novel biomarkers for the detection of wound infection by wound fluid RT-PCR in rats”

“Oxidative stress mediates skin fragility in obese diabetic mice”

“Health-related quality of life and associated factors in patients with primary lymphoedema”

“Development and evaluation of new product for male urinary incontinence care using pouch”

“A qualitative study of morphological characteristics and wound healing process in venous leg ulcers”

Research activities

1. Activity policy

Our gerontological nursing researches are focusing on elderly suffering with geriatric syndrome such as pressure ulcers, incontinence, malnutrition, pain, dysphagia, osteoporosis and dementia. Our wound care management researches are focusing on pressure ulcers, diabetic foot ulcers, ulcers with peripheral vascular diseases and malignant fungating ulcers.

Majority of our clinical researches are conducted at the University of Tokyo Hospital as a main field. We are participating in pressure ulcer ward rounds as members of the Pressure Ulcer Team of the hospital. We also attend the Foot Care Outpatient Clinic held by Department of Metabolic Diseases, and the Stoma Outpatient Clinic held by Department of Urology and Department of Colorectal Surgery. We also actively perform epidemiological and clinical researches in the related institutes other than the University hospital, so that our research is always based on clinical practice.

Our special research missions in 2010 were twofold:

(1) We aimed to develop our research system within our department as a sequential flow of “translational research,” from the basic biology, through engineering

by industry-academia cooperation, and to the establishment of clinical evidences returning the achievement of our research to the society. Some of the studies described below were performed in this direction.

(2) Development of new nursing devices requires involvement of engineering specialists. We have invented a number of nursing products and equipments based on our research by academia-industrial cooperation. In October, the new endowed department, the Department of Life Support Technology (Molten), was established under intimate collaboration with our department, where Dr. Taketoshi Mori, a specialist of bioengineering, was invited as the Project Associate Professor. We have started to develop life support technologies based on new engineering concept, together with this new department.

We held the 6th University of Tokyo Open Seminar of Advanced Wound Care on November 2010 at Yasuda Hall, entitled “Expectation for the new nursing position in the field of wound, ostomy and continence nursing: Development of an advanced wound nursing education.” We had a fruitful discussion regarding the significance of the novel nursing position and the future nursing in Japan 20 years later, through the evidence based on our research and the practice in the other country.

Our international research activities include a leadership of Japanese Society of International Lymphoedema Framework (ILF), a international group for lymphoedema management. We conducted epidemiological research of the primary and secondary lymphoedema, under the collaboration with Prof. Christine Moffatt (Glasgow University, UK), the head of ILF. Especially, international research of effect of lymphoedema and its treatment on the health related quality of life has been executed with British and French researchers. Further mission regarding lymphoedema was an invitation of Dr. Hans Pritschow (the head of the center of manual lymph drainage, Germany), an internationally well-known therapist of the manual lymph drainage (MLD) and combined decongestive therapy (CDT). We held an international session including a lecture and a therapy demonstration to lymphoedema patients by Dr. Pritschow.

2. Research fields and themes in 2010

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
- Establishment of the animal model of pressure ulcer of deep tissue injury type and elucidation of its pathophysiological mechanisms
- Skin vulnerability and aging in the metabolic syndrome model mice
- Cutaneous wound healing and diabetes mellitus
- New animal model of wound infection
- Mechanisms of skin maceration

2) Nursing engineering

- Development of a new air-mattress equipped with interface pressure sensing system and automatic pressure control
- Non-invasive detection of tissue injury and pre-injury status using ultrasonography and thermography
- Development of a handy type kit for diagnosis of wound infection

3) Clinical studies

- Cross-sectional study of diabetic foot (callus, fissures, onychomycosis etc.) and its risk factors
- Evaluation of wound nutritional status in elderly with pressure ulcers
- Risk factors of venous leg ulcers and fungating breast cancer
- Survey and international comparison of lymphoedema (collaboration with International Lymphoedema Framework)
- Clinical outcomes and cost-effectiveness of WOC nurse practice with advanced education and discretion
- Evaluation of a new concept diaper for elderly people for incontinence associated dermatitis management
- New assessment technology of the aged skin by engineering analysis.
- Thermographic assessment of the foot circulation based on the concept of angiosome
- Establishment of a novel diagnosis method of latent dysphagia

Several awards were given to our research as follows.

“Mechanisms of regulation of MMP expression by quorum sensing signals of *P.aeruginosa*.” Dr. Gojiro Nakagami (Lecturer) won the research prize of the 40th Annual Meeting of the Japan Society for Wound Healing.

“Skin bacterial contamination around the coccyx and the urethra under the circumstance of pad use.” Dr. Gojiro Nakagami (Lecturer) won the congress prize of the 25th Annual Meeting of Japanese Society of Geriatric Urology.

“A preliminary study of estimation of exudate volume from the full-thickness pressure ulcers: Versatility of DESIGN-R.” A doctor course student Shinji Iizaka (The DC2 Research Fellow of Japan Society for the Promotion of Science) won the best paper prize of the 19th Annual Meeting of Japanese Society of Wound, Ostomy and Continence Management.

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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 evidence base of global health programs through the provision of 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.

The priority areas of research are:

- Health outcome research (mortality, morbidity and disability, health services, cost-effectiveness of interventions, disease modeling, resource flows, and impact evaluation, including tracking the progress towards the Millennium Development Goals and contribution to the Global Burden of Disease study);
- Health system performance assessment, including the analysis of health system inputs (financing, human resources), outputs (service delivery, effective coverage), and impact (health status);
- Health and foreign policy (e.g. global health architecture and governance, G8 and global health, donor commitments).

Finally, the fundamental role of the department is to produce the next generations of leaders in global health.

Education

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 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 2008;

1. Global health policy: overview
2. MDG4
3. MDG5
4. MDG 6 (HIV/AIDS, Tuberculosis, Malaria)
5. Acute disease surveillance
6. Non-communicable diseases
7. Global health policy: 30 years since Alma Ata
8. Burden of disease and risk factor assessment
9. Human resources for health
10. Priority setting
11. Health financing
12. Global health challenges

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

Strengthening health systems to achieve MDG 4 and 5. Research on Global Health Issues, Health and Labour Sciences Research Grant

Epidemiology of HIV/AIDS: A cohort study and meta-analysis. Research on HIV/AIDS, Health and Labour Sciences Research Grant

Inclusive proof research on health medical care of our

country, Health and Labour Sciences Research Grant

Genetic analysis of tuberculosis epidemiology. Scientific Research (B), Grants-in-Aid for Scientific Research.

The WHO Multi-country Survey on Maternal and Newborn Health. World Health Organization

Multicenter study concerning the improvement of the outcome for newborn baby's serious illness. Health and Labour Sciences Research Grant

Research on role and possibility of diagnosis and treatment guideline for EBM spread promotion in the future. Health and Labour Sciences Research Grant.

Grand design of child health and development research. Child Health and Development Research Grant.

Development and application of statistical technique for correction of systematic measurement error margin in health statistics. Grant-in-Aid for Young Scientists (B).

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Department of Community and Global Health

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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 (1999-2005), 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 the 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 activate community-based activities and how to link bottom-up approach to national and international policy. The department currently consists of: our Department Chair and Professor, 3 Assistant Professors, 10 Visiting Lecturers, 20 PhD course

students, 27 Master's course students, 4 research students, and 17 visiting researchers. About 40% of the students are international students.

International Cooperation Activities

Among our international cooperation activities at the global level was a human security project conducted in collaboration with the Japan Center for International Exchange (JCIE). Designed to promote Japan's contribution to global health, the Working Group on Challenges in Global Health and Japan's Contribution (September 2007 - July 2009) was ultimately reformed/strengthened into the Global Health and Human Security program. Within this framework, we have conducted activities to facilitate policy discussions among national/international global health personnel and to strengthen concrete policy implementation.

In concrete, we attended the JCIE/UN Seminar on Health and Human Security held in New York in May 2010. Furthermore, we will play a leading role in the "health and human security" project, which has been initiated in Africa, Central/South America, and Asia.

We also contributed to planning the Second Global Forum on Human Resources for Health

organized in Bangkok in January 2011, in which the Japan International Cooperation Agency (JICA) was also involved. Our efforts were also made to develop a position paper related to health workforce for the first Global Symposium on Health Systems Research held in Montreux, Switzerland in October 2010.

We also provided technical support to projects run by the JICA and NGOs in Lao PDR (medical education), Thailand (HIV/AIDS education for labor unions), and Vietnam (safe water and better nutrition), and have conducted research in collaboration with the Cambodian government.

Teaching Activities

The main objective of our teaching activities is to train compassionate global health leaders. In concrete terms, we aim:

1. To train future leaders in the field of global health targeting careers with the United Nations, the Global Fund, JICA, and civil societies;
2. To train academics with the potential to become leaders in global health in universities or research institutes.

Major areas covered by our educational curriculum include: 1) Global health, 2) health promotion, 3) school health in developing countries, 4) community-based health interventions, 5) social capital, 6) medical anthropology, and 7) reproductive health.

Our department has accepted students of various backgrounds and disciplines: medical doctors, nurses, co-medical workers, social scientists and others. The academic year for the Master's course (MA, 2 years) as well as the Doctor's course (PhD, 3 years) starts in April and ends in March every year. All lectures and seminars are conducted in English.

Even outside school, we were also involved in education for JICA trainees from abroad and made several lectures at other universities during the academic year 2010. In addition, we made a lecture on "safe water" in a public lecture (for the general public) held by our university. In addition, by the request from the Japanese government, we lectured on "safe water in developing countries" for high school students, participating in the Asian Youth Exchanging Program.

Research activities

The Department aims to contribute to policy making and promoting actions for better health by making the best use of community-based research. We carry out research by working in tandem with different international organizations, NGOs, and universities in developing countries. The major directions of current research have encompassed primary health care, health promotion, school health, health and human rights (including migrants' health), human security, conflict and health, injury prevention, HIV/AIDS, tuberculosis, malaria, neglected tropical diseases, and nutrition among others. Our research has been conducted in various countries, including Nepal, India, Myanmar, Thailand, Bangladesh, Viet Nam, Lao PDR, Cambodia, Mongolia, Ghana, Tanzania, Kenya, Zambia, and Peru.

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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 one professor, one associate professor, three research associates, 13 graduate students, 3 research fellows, and 7 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 microsatellite 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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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 1992 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 associates, one assistant clerk, one technical assistant, fifteen visiting lecturers, thirteen visiting researchers, and fifteen graduate students, including seven 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, Germany, Greece, China, Taiwan, Korea, Thailand, Viet Nam, Laos, Malaysia, Bangladesh, Pakistan, Sri Lanka and Russia, 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) Medical microbiology and zoology
 - 3) Maternal and child diseases
 - 4) Immunology
 - 5) Maternal and child health
 - 6) School health and nursing
 - 7) International health
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 and acute encephalopathy with febrile convulsive status epilepticus.
- (2) Studies on developmental brain disorders caused by abnormal intracellular signal transduction, such as tuberous sclerosis, Noonan syndrome and Costello syndrome.
- (3) Molecular genetic and cell biologic studies combined with post-genomic approaches on molecules regulating neuronal migration, such as Doublecortin and Cdk5.
- (4) Molecular pathologic studies on childhood intractable epilepsy and developmental disorders, such as West syndrome and Rett syndrome, using genetically engineered animals.
- (5) Molecular genetics and biochemistry of inherited metabolic disorders, such as peroxisomal disorders, and of neurodegenerative diseases, such as spinal muscular atrophy.
- (6) Pharmacological studies on the pathogenesis and treatment of developmental disorders, such as attention deficit/ hyperactivity disorder, using genetically engineered animals.
- (7) Molecular epidemiology of pediatric infectious diseases, in particular viral diarrheal diseases (rotavirus, norovirus, adenovirus, sapovirus and astrovirus) and HIV infection.
- (8) Epidemiological studies on nutrition and child growth.
- (9) Studies on the epigenetics of the fetal origin of adult diseases.
- (10) Effects of high-rise living on physical and mental development of children.
- (11) Epidemiological studies on the mental health of schoolchildren, and of mothers and children living abroad

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Department of Human Ecology

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Introduction and Organization

We had four research/teaching faculties in FY2010. Apart from the faculty staffs, two secretaries, four doctoral candidates (two foreign students), seven master course students (including four foreign students), one post-doctoral fellow and three research fellows are working in the department. There are ten extra-university lecturers delivering lectures in either graduate or undergraduate course. Prof. Watanabe holds the additional post in the Transdisciplinary Initiative for Global Sustainability (TIGS).

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. 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 Health Sciences and Nursing, providing the lectures on “Human Ecology”, “Environmental Health”, “Demography”, “International Health”. We were also responsible for organizing “Pharmacology and Toxicology”, “Physiology”, “Anatomy”, 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.

As a part of the Global30 program, staff made a site visit to Australia National University, where they are running a Human Ecology program with a high proportion of foreign students and exchanged information regarding the operation of such a program.

Research activities

Most of our researches focused on the field of “Environmental Health” and/or “Population ecology [of human]”, and we utilized both fieldwork and experimental approach. The areas for the field studies were mainly Asian-Oceanian rural 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. What follows is a list of major activities conducted in the past two years.

1. Evaluation and Alleviation of Environmental Burden due to Subsistence Transition in Asia-Pacific –Elucidation of Health Impact:

Most communities in Asia-Pacific undergo a very rapid transition from traditional subsistence to cash-economy agriculture. Such transition entails introduction and release-accumulation of chemical substances, such as pesticides and food additives (through the purchase of processed foods), into the local ecosystem, which in turn would affect not only the health and survival of the inhabitants, but also the safety of local produce. Choosing six regions that represent diversified environments in Asia-Pacific, we (1) describe such transition and their environmental consequences in detail, (2) investigate the interrelationship between the transitions and the changes of local chemical environments, and (3) examine their health impact among the individuals in the target areas. Final goal of the study will be to make a policy recommendation to minimize unnecessary adverse effects of such transition. The analyses of the collected samples have been progressed, and the data analyses are still going on. Part of the results had been presented in some international conference such as ICHE in UK and ESA in USA, 2009 and 2010.

2. Development and subsistence activity, subsistence transition and adaptation:

In many Asian and Oceanian countries, various types of developmental projects have been undertaken aiming at economic development, procurement of natural resources, or accelerating tourism. Such developmental projects brought about drastic changes in the subsistence activity of people, availability of natural resources, or ecosystem, and in turn, caused changes in lifestyle and health status, disease patterns of the people. Attempts to describe such changes from the viewpoint of political ecology were made in China as well as Papua New Guinea. Adaptive strategy at household level was analyzed in China, where

subsistence transition has been taking place, and possible determinant of the difference in the strategy was identified. In some studies, spatial information technology, such as Geographical Information System (GIS)/GPS, and spatial statistical methods were applied for analyzing the relationship between the subsistence transition and land-use.

3. Human Ecology related with regional sustainability issues in Asian urban and rural communities:

We have participated in a water-reuse project conducted in a suburb area close to Bangkok, Thailand, in which we are in charge of developing an appropriate method/protocol for health risk assessment. We have carried out a survey on the site selected last year, regarding the pattern of water use as well as attitude towards the potential use of reclaimed water. The results showed heterogeneity in both water consumption and attitude towards reclaimed water within relatively small geographical area, which might be related with the proximity to the industrial area.

In West Java, Indonesia, we did a survey regarding the system for health information gathering and regarding activities associated with environmental health. Discussions and information exchange were conducted with local stakeholders to extract the urgent health issues in the locality in relation to regional sustainability.

In a suburb of Dhaka, capitol of Bangladesh, exposure to lead (Pb) among the school children was evaluated, and the relationship between a genetic polymorphism and the effect of Pb on blood ALA (a toxicity biomarker of Pb) was evaluated. Gender-associated difference in Pb exposure and in genetic susceptibility were identified among this children's population.

4. Studies on nutrition, growth, and physical activities (energetics) in developing countries:

In rural Bangladesh, arsenic contamination of the drinking water has been creating a huge problem. We have been focusing on modifiers of arsenic toxicity, including sex or nutritional status. We are focusing on the effects of oral contraceptives as well as some genetic polymorphisms in As-metabolism pathway.

5. Neurodevelopmental effects of perinatal exposure to environmental chemicals:

The fetus/newborn is said to be relatively sensitive to many of the environmental chemicals. We focused on the exposure to chemicals during perinatal period. Using cultured neurons, effect of bisphenol A, a typical endocrine disrupting chemical, has been examined. In addition, the basic action mechanism of such estrogenic chemicals have been examined and reported.

6. Role of selenium in a population highly exposed to methylmercury through fish consumption:

Relatively high concentration of methylmercury (MeHg) can be found in some predator fish species through food chain, and health risks associated with excessive consumption of such seafood items have been debated long time. On the other hand, fish is very important source of some nutrients including protein, polyunsaturated fatty acids, and minerals, and some of these nutrients might interfere with MeHg toxicity. We have collaborated with other institutes like National Institute for Minamata Diseases who conducted a survey in a fish-eating population in Japan, and examined the nutritional status of selenium, a micronutrient for which fish provide substantial amount.

7. Prediction and adaptation measures for health risks due to climate change and/or air pollution:

Concerns are growing over the potential health effects of climate change, especially global warming, as well as of air pollution, especially long-range pollution that could occur beyond national borders. In collaboration with the Atmosphere and Ocean Research Institute as well as National Institute of Environmental Studies, we are trying to develop a health risk map in a small-scale range like Kanto plane, taking advantage of the climate prediction models using assimilation technique. During this year, basic information about the relationship between temperature, air pollutants and various health effects has been collected, which will be fed into this climate model.

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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. Prof. Kita has moved from The Institute of Medical Science, The University of Tokyo on March 1st, 1998.

Teaching activities

Teaching activity 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: Biochemistry and Nutrition I, II

This course is comprised of lectures and seminars to provide basic concepts and newer vistas for understanding nutrition 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,

Physiological Chemistry, Nutrition, Medical Chemistry, Practice on Medical Chemistry, Parasitology.

Research activities

Energy metabolism is essential for the survival, continued growth and reproduction of living organisms. From the standpoint of biological adaptation, we have been studying on the molecular mechanism of energy transducing systems such as mitochondrial and bacterial respiratory chain. In addition, we are interested in the basic biological reactions such as protein synthesis. Our research have been focusing on

I. Human mitochondria

- 1) succinate-ubiquinone reductase
- 2) mitochondrial myopathy

II. *Ascaris suum* and *Caenorhabditis elegans*

- 1) molecular mechanism of adaptation to low oxygen tension (regulation of gene expression of mitochondrial proteins)
- 2) mitochondrial fumarate reductase (structure function relationship, enzyme evolution)
- 3) *C. elegans* as a model system of parasitic nematode (expression of foreign genes or cDNAs, gene knockout)

III. Parasitic protozoa (*Plasmodium falciparum* , *Trypanosoma brucei*, *Trypanosoma cruzi*, *Cryptosporidium*)

- 1) characterization of mitochondria as a target for the chemotherapy
- 2) molecular biology of mitochondrial DNA
- 3) structure based drug design (SBDD)

IV. Protein synthesis

- 1) Mitochondrial protein synthesis
- 2) Biogenesis of cytoplasmic ribosomes

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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 recently important topics in epidemiologic research. Epidemiologic data are of course needed for conducting the assessment of certain treatment including medicine and estimating situation of disease development.

Epidemiology not only provides research methodology in the field of public health but also is considered a practical study for public health and thus a central field of health science. However, both education and research systems have long been insufficient in Japan.

Social and preventive epidemiology is a study of epidemiologically clarifying the relationship between various phenomena in human society (including individual lifestyle) and certain disease.

The Department of Social and Preventive Epidemiology particularly focuses on nutrition, which

is essential for individual and population health, as a main research topic and epidemiologically researches various issues related to nutrition (nutritional epidemiology), playing a central role in this research field in Japan.

The Department currently consists of one professor and one associate.

Teaching activities

We have the following two lectures in the School of Public Health.

Epidemiological research and practice
Practice and assessment in public health

Both are strongly associated with practical tasks in public health field, aiming at giving students opportunities for acquiring abilities of conducting public health activities and tasks based on theory of epidemiology.

We have also several lectures for students in other schools.

Research activities

Our main topic is basic research for development and application of research methodology in the field of nutritional epidemiology. Based on this basic research, we also conduct a wide range of epidemiologic research for investigating the relationship of nutrition

with health and disease. As a characteristic of this research field, we conduct many multi-center studies with various kinds of disease.

Another characteristic is collection of research findings (scientific papers) derived from epidemiologic research all over the world on the association of nutrition with health and disease, which is applied for health control through nutrition improvement and disease control.

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Introduction and Organization

The Department of Health Economics and Epidemiology Research is a new department established since 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 health care system/policy for further improvement of the quality of health care in this country. For this purpose, the Department puts a unique emphasis on quantitative analytic methods and inter-disciplinary theories across economics, epidemiology, and other social sciences.

Teaching activities

Under the MPH program, the Department is responsible for 5 courses, two on clinical epidemiology and the other three on health economics. 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 statistical inference. Then, the course requires participating students to apply the provided knowledge to empirical examples such as evaluation of effectiveness of screening tests, pharmaceutical

cost-effective analysis, technology assessment of surgical treatment, and hospital management. In the applied course, the students are required to set a research hypothesis, design a study, and prepare an own study protocol for fund proposal. The lecture course on health economics provides an overview of health care systems in this country and a systematic review on basic micro-economic theories and cost-effectiveness analysis. The applied course offers the students an opportunity for hands-on training of actual economic evaluation of health care and technologies.

A new course starting in 2009 takes up hot topics in health policy such as physician deficiency, and encourages students to debate strictly based on available empirical evidences.

The Department accepted 4 doctoral student and 2 master students for the fiscal years of 2010.

Research activities

Current activities in this Department cover a broad range of health services research, including clinical studies, economic evaluation of health technology and health policy, quality of life research, hospital administration and quality assurance, and social epidemiology research.

Consultation for design, data collection, and analysis of clinical studies are provided for several clinical studies, mainly in cardiovascular arena. In the collaboration with the Department of Health Management and Policy in 22nd Medical Research

Center in the University of Tokyo Hospital, the Department has also contributed to the development and refinement of 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 data sources such as the Patient Survey, and hospital financial statement. Socioeconomic status affects people's health, which is another research focus in this Department. The Department has contributed to an ongoing panel survey on socioeconomic status and health among elderly (Japanese Study of Ageing and Retirement; J-STAR) since 2007 and the young adults (Japanese Study of Stratification, Income, and Neighborhood; J-SHINE) since 2010, in the collaboration with other established research institutes.

Since health care services should be delivered efficiently under the publicly funded health care system, economic evaluation of new health care technologies is one of the research topics in the Department. Molecular target therapies of cancer, which are effective but costly, attract the great concern. Based on the modeling of therapies and efficacy data in clinical trials, cost effectiveness of the therapies have been evaluated. Preventive services such as smoking cessation therapies are also important field for economic evaluation. We also contribute for the piggy bag style data collection for economic evaluation in the clinical trials and epidemiological prospective studies. Standardized methods of data collection for both costs and outcomes in economic evaluations should be established through these activities. If the result of economic evaluation would be used as the reference for coverage decision of new technologies under publicly funded health care system, acceptable thresholds of payment must be discussed. International comparative survey was conducted to see people's willingness to pay for additional year of life in perfect condition.

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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.

Whereas health communication is a major discipline in the USA and there are many such graduate programs, our department offers one of the only two health communication programs in Japan. However, the importance of the health communication discipline has gradually been recognized among the academic society as well as among general public.

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. Theories in Health Communication
3. Science Communication
4. Communication during Emergency and Disaster
5. Patient-provider Communication: Patient Perspective
6. Communication Skills for Health Care Providers
7. Mass Media and Communication: Television
8. Internet Communication
9. Mass Media and Communication: News Paper
10. Social Marketing
11. Methodology of Health Communication Research
12. Health Communication Campaign
13. Patient-provider Communication: Provider Perspective

[Health Communication Practice]

1. Coaching
2. Manners in Interpersonal Relationship
3. Internet: Research, Analysis and Evaluation of Websites
4. Internet: Website Development
5. Practice of Media Publicity
6. Evaluation of News
7. MBTI (Myers-Briggs Type Indicator)
8. Image / Film Development

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 healthcare 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, telemedicine, 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

Department of Social Gerontology

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Introduction and Organization

It is often voiced from the general public that recent advancement of medicinal technology would not necessarily lead to the happiness of people: Life prolongation technology enables even the terminally ill to live for a considerable period. How to use the technology is a serious problem in clinical practice. Also, there is evidence that the prolongation of life expectancy for the elderly does not mean the prolongation of health and productivity, but that of morbidity. Taking another example, we are experiencing ethical dilemmas with the application of medical technology such as genetic screenings and organ transplantation. When we turn to the worldwide situation regarding health, we will find poverty and unequal distribution in terms of health resources and outcomes.

The department is studying these health-related problems from social perspective, many of which are often difficult to decide upon. Major topics include elderly health, terminal care, medical ethics and international health among others. We are currently conducting several research projects as described below.

Our educational activities include lectures, practical training and supervision of writing theses for students in graduate level as well as undergraduate level. The

department consists of one professor, one lecturer, one associate, 25 visiting researchers and 7 graduate students (including two international students from Korea and Philippines).

Teaching activities

1. Graduate Courses, School of Health Sciences and Nursing
 - 1) Social Gerontology: The course is to provide the students with the basic understanding of social sciences in the field of gerontology. The topics include (1) the concept and measurements of quality of life, (2) the influences of psychosocial factors on health status, health behavior and health belief, and (3) policy considerations for medical care and prevention.
2. Undergraduate Courses, School of Health Sciences and Nursing
 - 1) Health Education: This course provides fundamental understanding in health education and health promotion in various settings such as community, workplace, school and clinics. Emphasis is put upon preparing students to conduct health education in their future career as a health professional.
 - 2) Practice in Social Surveys: This is for practicing

to conduct social surveys using questionnaire/interview method. The students are divided into several groups, and each group is given a survey area. They will go through all the processes of a health sociological survey, from planning the survey to writing a report based on the survey. They have the opportunity to report and discuss their surveys with each other.

- 3) Health Behavior: This seminar aims to help the students to practice the basic research methods related to health behaviors. Final product will be a research proposal and the review of relevant literature.
- 4) Decision-making in Health: This course introduces students to recent developments in medical and health decision-making. Topics include the definition and measurement of quality of life (QOL), cost-effectiveness and cost-benefit analysis, technology assessment and optimal allocation of scarce medical resources. Readings are selected from extensive range of literature in behavioral sciences, economics and philosophy as well as medical decision-making.

Research activities

- 1) Reciprocity of Social Support on Subjective Well-being of the Elderly: Traditional support study emphasizes the importance of receiving support. We examine the pattern of support exchange (i.e., receiving and providing) and its effects on the subjective well-being of the elderly in rural Japan as well as a number of Asian countries such as Korea, Nepal, Malaysia, and Indonesia. Intervention studies regarding intergeneration exchanges and targeting the relocated elderly are now in progress.
- 2) Disability-free Life Expectancy in Japan: We calculate disability-free expectancy using a large-scale cohort of the residents in Nagano Prefecture and examine variables influencing the life expectancy.
- 3) Multi-disciplinary Collaboration in the Psychosocial Care for the People with Cancer in Clinical Setting: The survey we performed indicated that Japanese surgeons considered

themselves mainly responsible for medical aspects of patient care and paid less attention to psychosocial issues. We examine the possibilities of integrating other support resources such as clinical psychologists, psychiatrists and medical social workers in the clinical practices of cancer in Japan.

- 4) Activities of Cancer Self-help Groups in Japan: Although cancer self-help groups are growing presence in Japan, they do not attract as many patients as they do in other countries such as US. Through semi-structured interviews and a questionnaire survey, we revealed how Japanese cancer survivors and surgeons view peer support activities implemented by cancer survivors.
- 5) Socio-cultural Analysis of Sexuality after Cancer: Researchers have long neglected sexuality after cancer. Through intensive semi-structured interviews with Japanese women with breast cancer, we examine how the cancer diagnosis and the following treatments have affected their sexuality and the whole relationship with their partners. Based on the findings of the qualitative approach, we intend to perform a large-scale survey on sexual complications among Japanese cancer survivors.
- 6) Role and Function of Ethics Committees in Japan: In this project, we surveyed and analyzed the role and function of ethics committees at various levels, from hospital level to national level.

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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. At present, the department has only one faculty member: Prof. Hiroshi Oyama, M.D., Ph.D. However, 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 Pharmacoepidemiology

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Introduction and Organization

As of April 2010, the Department of Pharmacoepidemiology consists of a professor (Kiyoshi Kubota), two associates (Takafumi Nishimura and Tsugumichi Sato), 3 teaching assistants, 2 clerical assistants.

The department was established as a donated department in April 1993 for a limited time of 3 years till March 1996. The department has been extended 5 times for 3-year period in each extension and the department is now in the 3rd year of the 6th period (March 2008-April 2010).

Pharmacoepidemiology is a new scientific field starting in 1980s. In Japan, Japanese Society for Pharmacoepidemiology was established led by Professor Tadashi Kusunoki who was the first Japanese professor of pharmacoepidemiology in the department between April 1993 to March 1996.

In the second period from April 1996 to March 1999, two pilot studies of Prescription-Event Monitoring in Japan were conducted. In the third period from April 1999 to March 2002, the department exerted a leadership to establish a non-profitable organization (NPO) Drug Safety Research Unit Japan (DSRU Japan). This Unit worked as the study office for two pilot studies on Prescription-Event Monitoring and also for a case-control study on the association between non-steroidal anti-inflammatory drugs and upper gastrointestinal bleeding. It also worked as the study office of other studies including clinical trials

led by researchers or those sponsored by a drug company or Ministry of Health and Welfare.

Teaching activities

The department is involved in the teaching activities inside University of Tokyo including Graduate School of Medicine and Faculty of Medicine and School of Public Health. The department also played a leading role to organize a 6-month course of “pharmacoepidemiology seminar” held by Union of Japanese Scientists and Engineers. This seminar is to educate those in drug companies, school of pharmacies of colleges and universities and those involved in administration in Pharmaceuticals Medical Devices Agency (PMDA). The first seminar was held in 2006. In 2010, the 5th seminar is being conducted.

Furthermore, the department has been a driving force to make a textbook of pharmacoepidemiology in Japanese published in 2010. The department is also contributing to translate a textbook by Dr Patric Waller, a former regulator in the regulatory body in the UK entitled an “An Introduction to Pharmacovigilance” which will be published sometime in 2011.

Research activities

Like other epidemiological studies, pharmacoepidemiology studies are those on people and the

study requires an organization which supports the study. NPO Drug Safety Research Unit established in 2001 has been working to support various studies including pilot studies of Prescription-Event Monitoring in Japan, a case-control study on the association between non-steroidal anti-inflammatory drugs and upper gastrointestinal bleeding, and handling of information on serious adverse event experienced in the investigator-led clinical trials.

The department and NPO Drug Safety Research Unit also studied the baseline incidence of Interstitial Lung Diseases (ILDs) in 328 patients with malignant mesothelioma by collaborating with doctors in 26 hospitals in the west part of Japan.

Since April 2010, the department has been recognized as a department to manage 'Safety Information Division' of Clinical Research Support Center of the University of Tokyo Hospital. The Center will be developed as the center for multi-institutional clinical trials.

The department developed a web-based system called as Safety Management system for Unapproved Drugs (SMUD) between 2005 and 2007 by the co-operation with the University hospital Medical Information Network (UMIN) to monitor the safety of thalidomide imported by individual doctors under the support of Ministry of Health, Labour and Welfare (MHLW). From 2009, the NPO worked as the bureau for the operation of SMUD which is needed even after the approval of thalidomide for multiple myeloma in 2008, as thalidomide is still imported by individual doctors because of the need to use thalidomide in treatments of diseases other than multiple myeloma and other reasons.

The department has been a driving force of another study called as "Japan Statin Study (JSS)", a joint research by Japanese Society of Pharmacoepidemiology and Japanese Society of Hospital Pharmacists, using a design of a case-cohort study and NPO Drug Safety Research Unit works as the study office.

Another research activity in the department is the research of the application of data-mining methodology to the analysis of spontaneous reports. The use of data-mining methodology in pharmacovigilance began in 1990 in WHO Uppsala Monitoring Centre, Food and Drug Administration in

the US and other regulatory bodies in the Western countries. Recently, Japanese Ministry of Health Labour and Welfare also decided to introduce the method into the regulation in Japan. The research in the department is to develop a new method to utilize the large data of Drug Use Investigation in the evaluation of spontaneous reports using the method of reporting odds ratio.

One of other research activities is on the use of electronic claims database. It is now clear that national claims database (NDB) in Japan is provided for the secondary purposes including researches from April 2011. Some relatively small data sources of claims data are already commercially available and the department started to search for the effective use of Japanese claims database. The department will start studies using NDB based on this experience.

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Department of Integrated Traditional Medicine

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Introduction and Organization

In an attempt to investigate the Japanese traditional herbal medicine, the Department of Integrated Traditional Medicine was established in 1996 as the Department of Bioregulatory Function affiliated with the Department of Medicine and Physical Therapy. In 1999, the Department of Geriatric Medicine joined us as another affiliated Department. Pharmacological actions by medicinal herbs have been intensively investigated not only on allergic or autoimmune diseases, but also the disorders associated with aging process. Therapeutic experiments of herbal medicine have been carried out by using animal disease models to clarify the mechanisms of the pharmacological actions. In additions, the biological actions of the herbs have been investigated at cellular levels to clarify the intracellular signaling pathways induced by the medicinal herbs.

In 2003, traditional medicine was introduced into core curriculum of medical education program. Since 2004, lecture of traditional medicine has been started in this university as an essential study. The lectures have been served by this department. For postgraduate education, seminars of traditional medicine have been held at the university.

To avoid the confusion of similar names in western medicine, the name of this department “Department of Bioregulatory Function” was changed to “Department of Integrated Traditional Medicine” in 2005. Together with the change in the department name, we

started the translational studies on the physiology and pathology of the traditional medicine to translate the traditional medicine into scientific medicine. It required not only the chemical or pharmacological studies but also the biophysical approaches. In addition, translation from scientific medicine into the traditional medicine has been also required for better understanding the integration of both medicine. For this purpose, free seminars “traditional medicine as a life science” have been started, in which we analyze and translate the scientific data into the traditional medicine and also try to integrate both medicines.

Another research interest has been focused on the anti-aging medicine used in ancient traditional medicine. Recently, hormone supplemented therapy has been tried for disorders associated with aging in Western medicine. Some herbs have been shown to exert their pharmacological actions through receptors for certain hormones. The studies on this theme have been intensively performed at the department.

Postgraduate students have been also engaged in both basic and clinical sciences. The department provides a wide-ranged clinical, training, and research services. The weekly official activities of our department are a journal club on Tuesday and research conferences on Thursday.

Clinical activities

We have outpatient clinics on Tuesday, Wednesday, and Friday in the Department of General Medicine.

The diagnosis is made by the western medicine using blood examinations and imaging studies. After the scientific diagnosis, patients are diagnosed based on the instructions of the traditional herbal medicine, and treated mainly with the medicinal herbs.

Teaching activities

As for under-graduate student education, our department takes a part in systemic lectures for the 4th year medical students. In systemic lectures, comprehensive presentation for the understanding of basic knowledge about the concept, pathogenesis, pathology, diagnosis and treatment is performed.

In systemic lectures, we also present clinical cases of representative cases, and try to discuss with the students several points for planning the diagnosis and treatment. Demonstration of some herbs and typical recipes is also served during the lectures.

Free seminars "traditional medicine as a life science" are served, in which we analyze and translate the scientific data into the traditional medicine and also try to integrate the idea from both medicines.

For international experimental educations, a special lecture on traditional herbal medicine and demonstration of acupuncture were given for foreign students from over 40 countries at Harvard Project for Asian and International Relations Tokyo Conference.

Postgraduate students are served with scientific education of molecular cell biology and biophysics.

As for the post-graduate clinical education, we provide clinical lectures regularly on the use of traditional herbal medicine.

Research activities

Our research field covers from clinical, pharmacological, biological, and biophysical activities of traditional medicinal herbs. We focus on the molecular mechanisms of cell functions and intracellular signaling pathways.

Traditional medicinal herbs such as Ginseng has long been used as an anti-aging agent in Asian countries. Our laboratory studies molecular mechanisms of action by such anti-aging herbs. Ginsenoside Rb1, a major constituent of Ginseng has been demonstrated to exert the biological action as a phytoandrogen.

Endocrinological activities of anti-aging herbs are investigated using various molecular cell biological approaches including biochemistry, immunochemistry, molecular biology, molecular genetics such as gene targeting and transgenic mouse approaches, molecular biophysics.

Much current interest is focused on the therapeutic potential of hormone replacement therapy (HRT). However, one of the major adverse reactions of HRT is considered to promote cancer growth. It is urgent for us to elucidate the mechanisms of action by the anti-aging herbs and to compare them with those of hormones. Subsequently, we compare the biological activities of the anti-aging herbs and their counterpart hormones. We have demonstrated ginsenoside Rb1 and icariin exert the biological activity through its non-genomic action on androgen receptors. Recently, we have demonstrated that cinnamaldehyde, a major constituent of cinnamon selectively stimulates progesterone secretion in human adrenal cells. Our studies are focused on endocrinological actions of anti-aging herbs which are exerted through their genomic or non-genomic actions of steroid hormones. The spinocerebellar ataxias (SCAs) are clinically and genetically a heterogeneous group of neurodegenerative disorders. At present, we have no effective therapeutic tools. SCA6 has been demonstrated to be an autosomal dominant cerebellar ataxia associated with small polyglutamine-dependent expansions in the alpha 1A-voltage calcium channel. Long-term remission of this genetic disease has been attained with medicinal herbs. The findings of our study imply the therapeutic potential of herbal medicine for this hereditary neurodegenerative disorder. Extensive investigations are under way to clarify the mechanisms. It has been also demonstrated that some herbs are effective against multiple sclerosis and neuromyelitis optica in our laboratory.

It has been reported that some herbal medicines may be effective for acute episodes of chronic nonspecific low back pain. Spondylolisthesis is one of the causes of low back or neck pain. Although surgical treatment is often performed for symptomatic spondylolisthesis, we have succeeded in herbal therapy for degenerative spondylolisthesis.

Physiology, pathology and therapy of traditional herbal medicine is based on the principle of the

characteristic systems biology. According to the guideline of the traditional herbal medicine, we have examined the clinical effect by systems therapy with medicinal herbs in patients with bronchial asthma and essential hypertension. Long-term remission has been obtained in both disorders. Extensive studies are under way to elucidate the mechanisms by which systems therapy exerts the therapeutic activities.

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Department of Metabolome

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※For this department, this year's text is the same as that published last year.

Introduction and Organization

Lipidomics became one of the prominent research fields in metabolomics through recent advances in mass spectrometry. Lipids are classes of molecules thought to be very important, not only as energy source or constituents of biological membrane, but also as functional molecules concerning the many regulation steps in biological process. Furthermore, recent research has revealed the roles of lipids, such as mediators of signal transduction and ligands of receptors. Thus analyses of these metabolites seem to be extremely important to understand global and basic biological system in the life in combination with other -omics data such as genomics, transcriptomics and proteomics.

Under such circumstances, Department of Metabolome was settled at February 1st, 2003 by the donation from Ono Pharmaceutical Company and Shimadzu Corporation. And this laboratory has been tightly supported by the Department of cellular signaling (Prof. Takao Shimizu). At 2008 it was decided to be expanded for additional three years.

Adding to Prof. Taguchi, Dr. Oda, who is one of the prominent readers in the international proteomics field, is engaged as an associate professor. Six research associates are engaged in lipidomics research. Adding to them, 5 collaborating researchers from other universities, institutes or companies, occasionally engaged in metabolomics research in our laboratory.

Teaching activities

Lectures on mass spectrometry, proteomics and metabolomics were given to 2nd year of undergraduate, master course for medicine, and graduate students. Also special lectures for graduate students of other faculty in this university have been occasionally operated.

Further, several technical seminars, and academic meetings on mass spectrometry in proteomics and metabolomics have been operated in The Tokyo University, The Faculty of Medicine. And we have been trying to advertise global analytical methods by mass spectrometry through consulting for faculty stuffs on every technical problems in this field.

Research activities

In lipidomics, techniques of mass spectrometry become very important. Furthermore, recent advances in mass spectrometry make it possible to get comprehensive analyses of lipid metabolites within the cells and tissues. Studies on lipidomics are essential to get further understanding of each physiological and biological function of proteins concerning lipid metabolism. In this process, studies on comprehensive profiling on lipid metabolites in the cells should be inevitable. In particularly, to identify real lipid substrates for enzyme proteins, lipid ligands for receptor proteins, and lipid metabolites for its carrier proteins, lipidomics by mass spectrometry is very useful.

Another aim of lipidomics is to identify lipid

molecules from MS data and get profiling patterns of alteration of these molecules under specific circumstances. In these analytical processes of profiling, elucidation of unknown pathway or exact lipid substrate specificity of new enzyme proteins can be investigated.

Molecular diversity of glycerophospholipids arises from the nature of the linkage and from the identity of the fatty acyl chain that is linked to the sn-1 and sn-2 carbon atom. In the analytical methods in lipidomics comprehensive s by mass spectrometry, adding to the and untargeted analysis, focused or targeted analyses for categorical components are very important.

It is very difficult to obtain exact identification of all metabolites even in the limited classes of molecules such as lipid metabolites. This is caused by different extraction efficiency of individual metabolites, different solubility in analytical solvents, different ionic efficiency and broad dynamic ranges of their existence in biological samples. Even in the case of proteomics, it is very difficult to detect small amounts of peptides or proteins in mammalian plasma because of very wide dynamic ranges of protein contents in plasma. This is exactly the same in lipid metabolites in most of biological samples.

For detecting minor but physiologically important lipid molecules, specified technical strategies should be applied in selecting the detection methods including choice of HPLC system with most effective columns and that of the most suitable MS system and collision conditions.

Since electrospray ionization (ESI) is a soft ionization method, each molecule in a mixture can be detected without any fragmentation. However, in general only the major peaks will be detected if the sample is injected as a mixture without any LC separation. One of the solutions to this problem is to use specific detecting methods, such as precursor ion scanning and neutral loss scanning; these scanning modes are often used for measurement of particular focused phospholipids.

Soft ionization in mass spectrometry has induced some paradigm changes in the applications of mass spectrometry in biological studies. Effective insight can be obtained by comprehensive analyses of metabolic molecules under genetically, environmentally or physiologically different conditions.

Matrix assisted laser desorption/ionization (MALDI) is essentially used as off-line methods, while ESI can be used as a flow system, and is easily combined with on-line separation systems such as HPLC or capillary electrophoresis (CE). Sensitivity of detection by ESI essentially depends on the concentration of molecules in the sample solution. Thus, for obtaining a highest sensitivity, it is very important to use low elution rate with small size of column. For this purpose, capillary or nano LC system combined with ESI has been used.

Concerning metabolic molecules as target of metabolome, individual molecular structures are mostly known and relations of each metabolite are well studied. Thus we can easily imagine their metabolic linkage from our former knowledge. From these circumstances, we will be able to get effective data from comprehensive analysis of metabolites by mass spectrometric analyses, for elucidating new function of enzyme proteins including substrate specificities. By ESIMS, selective analyses of individual molecules in the mixture can be effectively obtained.

To elucidate the function of lipids, it is necessary to analyze not only their classes but also their molecular species. Thus, the application of mass spectrometry (MS) has become increasingly popular in the lipidomics. As analytical methods for lipidomics, we selected several different approaches in the identification of lipid molecular species. First one is a shotgun LC-MS/MS analysis with data dependent scanning for global identification of lipid molecular species, the second one is a structure-related focused method such as precursor ion scanning or neutral loss scanning. The third one is a sort of targeted method in combination with theoretically constructed MS/MS database of lipid search using multiple reaction monitoring. We constructed this method for detecting minor lipid metabolites such as oxidized lipids. Even, in this case structural isomers with same m/z value can be separately detected with partially comprehensive manner. The choice of these three different types of methods seems to be very important for detecting different class of lipid metabolites. Data from both first and second types of analyses can be subjected to our search engine, "Lipid Search" (<http://lipidsearch.jp>), and most probable molecular

species can be obtained with their compensated ion intensities. And identified individual molecular species can be automatically profiling according to their compensated ion intensities.

Recently, the global analysis of the oxidized fatty acid was also established in our laboratory, using theoretically expanded multiple reaction monitoring with reversed-phase liquid chromatography/tandem mass spectrometry. And this system has been effectively applied several biological samples, such as in the acute peritonitis model and the bronchial asthma model, for analyzing a quantitative variation of the oxidized fatty acid.

Our recent projects are clarifying the changes in profiling of lipid metabolites in obesity and inflammation.

Instruments for mass spectrometry

We have been using several ESI-MS instruments for metabolomics and proteomics; as triple stage quadrupole MS, 4000Qtrap and Quantum Ultra, and as iontrap, LCQ and LTQ, then as hybrid type-MS, LTQ Orbitrap, Q-TOF micro and LCMS-IT-TOF. Further as MALDI MS, we have been using AXIMA-CFR. Also at 2007, we started to prepare several new techniques for the elucidation of analysis in localization of lipid metabolites, such as razor microdissection, DESI and MALDI mass imaging.

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Department of Clinical Epidemiology and Systems

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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 lead by Professor Ryoza Nagai at the Department of Cardiovascular Medicine, because the unit had been terminated its five-year program supported by the Japan Science and Technology Agency in 2007 as scheduled.

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 is concurrently 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 associate professor 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 Pharmacoepidemiology.

Also, professor Yamazaki is a member of ethics committee in graduate school of medicine and faculty of medicine, the University of Tokyo, and associate professor 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 2010, we received 50 requests and made 2810 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

As “Introduction of Clinical Medicine” by

Department of Clinical and Genetic Informatics and related departments, professor Yamazaki and associate professor Koide gave lectures at the Large Conference Hall of our Inpatients' Ward A on April 9, and on 23 in 2010 respectively.

Also, the basic lectures of Medical Writing took place at the auditorium in Pharmaceutical Sciences Research Building as an intensive course on September 2-3 in 2010, 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, a lecture for "Current States and Issues of Large Clinical Trials" was held at Yokohama City University Graduate School of Medicine on January 26 in 2010. Also, a special lecture for "Clinical Pharmacology and Bioinformatics" was given to the fourth-grade students at Hamamatsu Medical University on February 2 in 2010.

Research activities

1) Studies of Clinical Epidemiology (Clinical trials, prospective cohort studies)

Our department facilitates large-scale clinical trials by executing the data management with our own computer servers and Japan Clinical Research Assist Center (JCRAC).

In particular, our department was in charge of the secretariat for Japanese Coronary Artery Disease (JCAD) study which was comparison of cardiovascular events between enhanced and normal therapy for hypertension/hyperlipemia patients with coronary narrowing, then improved the quality of trials without any difficulties. Furthermore, we takes the role of data management including training CRC in EMPATHY study and J-ART study, and both of them are randomized controlled trials

And studies for clinical epidemiology, such as monitoring blood pressure at home by using IT and investigational researches into new bio-markers for arteriosclerosis have been carried out by analyzing the database in the Center for Epidemiology and Preventive Medicine.

2) Improving Quality of Health Care

As a member of the quality improvement and assessment committee and chairs of the clinical pathway committee and the committee for quality care at our university hospital, associate professor Koide contributes to develop clinical pathways for clinical professionals and patients and hold a large conference of clinical pathway, and to assess our quality care by ourselves, etc..

3) Standardization of Information in Clinical Epidemiology

As attending the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and Health Level Seven which is one of the international standards development organizations, we study on electronic standards for the transfer pharmaceutical regulatory information, especially focusing on electronic standards for safety reporting. Also, through activities of participating in Clinical Data Interchange Standards Consortium (CDISC), we tackle the interoperability of information on clinical trials.

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Department of Ubiquitous Preventive Medicine

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Introduction and Organization

As an official department in the Graduate School of Medicine of the University of Tokyo, the Department of Ubiquitous Preventive Medicine was inaugurated in August 1st, 2007 (Heisei 19), with a generous donation from three pharmaceutical companies, Toa-Eiyo Ltd., Shionogi & Co., Ltd. and NEC Corporation to the University. Its predecessor is the Clinical Bio-Informatics Research Unit in the Graduate School of Medicine of the University of Tokyo (Director: Ryozi Nagai) which was established in 2002 (Heisei 14) 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 mission and services were continued by the Department of Ubiquitous Preventive Medicine 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. In August, 2010 (Heisei 22), our new mission of 5 years has started under the contribution of Shionogi & Co., Ltd.

The first head of the Department of Ubiquitous Preventive Medicine is Toru Suzuki, appointed in August 1st, 2007, as Associate Professor. Kenichi Aizawa serves as Research Associate.

Our objectives are to develop diagnostic biomarkers and diagnostic/therapeutic systems for prevention and early detection of disease. For this purpose, advanced and highly efficient techniques of proteome analysis are used with potential clinical application to preventive medicine. We are also committed to developing surrogate biomarkers for the discovery of drugs used in the treatment of cardiovascular diseases as well as the optimization of their efficacy, and to develop information infrastructure technologies for advancing personalized medicine by clinically applying the techniques of proteome analysis in an effort to promote preventive medicine for health promotion. Our mission is to ultimately establish the academic basis for Ubiquitous Preventive Medicine.

Our department provides diagnostic/therapeutic as well as academic support for the Department of Epidemiology and Preventive Medicine 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

The principal objective of our research is to develop diagnostic technologies for prevention and early detection of disease by using advanced and highly efficient techniques of proteome analysis, focusing on

the development of diagnostic biomarkers and diagnostic/therapeutic systems. A typical example is metabolic syndrome which if left untreated may result in lifestyle-related diseases including cardiovascular diseases. While cardiovascular diseases have a very long incubation period, protein modifications such as processing and denaturation play a leading role on the development of the diseases. Prevention is therefore of utmost importance. To this end, we are in the process of developing methods for the measurement of protein modifications in cardiovascular diseases and other new bio-tools for early detection of lifestyle-related diseases.

Specifically, the development of diagnostic biomarkers and diagnostic/therapeutic systems by using the techniques of proteome analysis is pursued on an ongoing basis with its main research projects being Industrial Technology Development for the New Energy and Industrial Technology Development Organization (NEDO) from 2007 to 2009 under the Ministry of Economy, Trade and Industry (METI) and Academic-Industrial Research Collaboration (joint research with Shimadzu Corporation).

In addition to the development of proteomics-based diagnostic methods, we also are developing information infrastructure technologies for advancing personalized medicine by clinically applying these methods to preventive medicine, as in comprehensive medical examinations. 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 and participatory 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 diagnostic/therapeutic 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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Department of Molecular Research for Vascular Diseases

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※For this department, this year's text is the same as that published last year.

Introduction and Organization

In late years, westernization of the life style and aging of the population advance in our country, and increase of the cardiovascular disease due to arteriosclerotic vascular change which is evoked by metabolic syndrome. Because its onset has been younger and is accompanied with the aggravation, the medical cost of cardiovascular disease traces the course of increase. It is the time point when the prescription for effective health resource redistribution is needed. The early detection and development of appropriate treatment for cardiovascular diseases are very urgent issues. This department was established in April 2008 for investigating the pathogenetic mechanism of vascular diseases associated with the metabolic diseases, supported by the division of cardiovascular medicine. Our main objective is to develop the fundamentals for finding the best method to protect vascular diseases.

Teaching activities

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

Each student can learn how to make a medical interview, check physical findings and make the actual plans for the diagnosis and treatment.

As for the post-graduate education, we have responsibility for some lectures concerning to hypertension and atherosclerosis.

Research activities

Our research field covers the molecular biology and physiology of the vascular system. We focus on the molecular mechanisms of the onset of atherosclerosis, especially endothelial dysfunction and inflammation due to metabolic disorders.

In order that blood vessels exposed to physical stress such as blood pressure or shear stress and various bioactive substances can maintain homeostasis, it is necessary to reduce the stresses, and in such a case the vascular endothelium needs to act against arterial sclerosis. In addition, it is known that control of growth and apoptosis in the neointima of the vascular smooth muscles is important for the development of an arterial sclerosis lesion.

On the other hand, the recent progress of adiposcience concerning the metabolic syndrome revealed the cardiovascular protective function of so-called 'beneficial' adipocytokine. A part of action mechanisms of adiponectin, representative of adipocytokines, is recognized to be caused by AMP-activated protein kinase (AMPK) and a part of its molecular mechanisms has been clarified. It was also reported that some diabetes remedies such as metformin or thiazolidine derivate have action to activate AMPK, suggesting a possibility that AMPK becomes the therapeutic target of a metabolic abnormality.

It is certain that AMPK is a kinase highly conserved from yeast to human, and performs an important action for organism when the stress is applied.

Hereafter, it is necessary to clarify the tissue-specific and stress-specific activation mechanism. Currently there are many unclarified facts, for example, why the action is different in cell-specific manner, as shown in the fact that AMPK acts for activation of PI3K-Akt in the vascular endothelial cells, whereas in other cells, the actions of AMPK and Akt are antagonistic to each other in many cases.

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Department of Advanced Skin Care (Miss Paris)

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Introduction and Organization

The Department of Advanced Skin Care (Miss Paris) was established in Graduate School of Medicine in April 2008. Current members include 1 visiting professor and 1 project research associate. The supportive departments are the Department of Gerontological Nursing/Wound Care Management and the Department of Life Support Technology (Molten).

Skin is a largest organ in the body with which the entire surface of the body is covered. Since skin functions as the front of body defense, a healthy skin is a base of the healthy life. Additionally, appearance of skin influences patients' mental health through their self images. With a rapid extension of the average life expectancy and an increase of lifestyle diseases (diabetes mellitus, obesity, metabolic syndrome etc.), many health related problems have occurred in Japan. Especially at the skin, which is always exposed to the external stimulations, the interaction of the external and inner factors has expanded a variety of dermatopathy. On such a skin, it is thought that the disruption of skin function has potentially occurred prior to manifestation of the pathological state. We are trying to establish "Advanced Skin Care" to detect and to recover the subclinical disruption of these functions promptly in order to achieve the healthier skin as a wellness promoting science.

One of our target is to investigate moderation role of skin. The barrier function and viscoelasticity are especially important for skin health. The former

prevents the moisture and electrolytes leaking from inside of the body, and obstructs the penetration of the foreign irritants into the body. The latter absorbs the mechanical force such as pressure, shock, and friction in defense of the muscle and bone. The viscoelasticity of skin is also important for smooth motion of joints. Therefore, these skin functions are the important target of intervention as the advanced skin care, and also are candidates of parameter to indicate the degree of skin health.

Practical methodology of care is our another main objective. Recently, several noninvasive technologies, such as thermography and ultrasonography, have been improved to be used handily at bed side. In addition to these technologies, we also focused on the skin color as a candidate indicator for skin health and systemic status.

On 17th January, 2011, the special lecture presented by Professor Masatoshi Abe, MD, Ph.D, Department of Dermatology, Gunma University Graduate School of Medicine, was held. More than 150 people including graduate students, nurses, dietitians, and estheticians, attended this special lecture.

Professor Sugama reported the progress of our research and spread the novel concept, Advanced Skin Care, in the educational lecture at 7th Conference of Soin Esthetic Association and in Presidential Lecture at 20th Annual Congress of Japan Society of Wound, Ostomy and Continence Management.

Teaching activities

We cooperated in the research relevant to the advanced skin care, which was conducted by the graduate students of the Department of Gerontological Nursing/Wound Care Management.

Research activities

With the object of establishing “advanced skin care”, we are conducting the translational research ranged from molecular and cellular biological approaches to clinical epidemiologic approaches. Our strategy is as follows;

- 1) Clarification of factors and mechanisms related to the degree of skin health,
- 2) Development of assessment tools and parameters to estimate the degree of skin health,
- 3) Development of skills and devices of “advanced skin care” to achieve the healthier skin.

We are focusing on the changes of the skin with the aging and lifestyle diseases, and have been making intense studies on the following four projects since 2009.

- 1) Morphological and functional analysis of skin in elder patients,
- 2) Structural and functional alteration of the macerated skin,
- 3) Characteristics of skin in lifestyle diseases (diabetes mellitus, obesity, metabolic syndrome etc.).
- 4) Development of novel technology for noninvasive skin assessment.

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Laboratory of Molecular Physiology on Energy Metabolism

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Introduction and Organization

The Laboratory of Molecular Physiology on Energy Metabolism was established in 2008, supported by the funds from Sunny Health Holdings and Sunny Health Co., Ltd., and is in close collaboration with the Department of Metabolic Diseases. The goal of this research program is to understand the pathophysiology of overnutrition-related diseases including metabolic syndrome and diabetes, the basis of which is considered to be insulin resistance closely associated with the imbalance of energy metabolism.

Teaching activities

Our department takes a part in systemic lectures for the master students in the Medical Science Graduate Program. In the lectures, comprehensive presentation for the understanding of basic knowledge about pathogenesis, pathology, diagnosis and treatment of diabetes and metabolic diseases is performed.

Research activities

We focus on the molecular mechanisms of insulin resistance, especially from the standpoint of lipid

metabolism.

For the better understanding of the basic pathogenesis of overnutrition and insulin resistance, we are proposing a new concept of “adipose capacity”; insulin resistance can be considered as a physiological response against the overload of nutrients beyond the “adipose capacity”. To clarify the molecular basis of this concept is one of our major goals.

The specific themes we are currently studying are as follows:

- 1) The elucidation of mechanisms of negative feedback regulation to understand the molecular basis of “adipose capacity”, especially from the viewpoint of the involvement of tumor suppressors such as p53.
- 2) The establishment of in vivo Ad-luc promoter analyses utilizing in vivo imaging system (IVIS).
- 3) The development of TFEL (transcription factor expression library) to entirely elucidate the transcriptional regulatory network of nutrient metabolism.
- 4) cis-to-trans (C2T) analyses of the transcriptional network based on TFEL.
- 5) The importance of the quality of fat besides the

quantity.

- 6) The new approach from chemical biology to the molecular physiology on energy metabolism.
- 7) The involvement of epigenetic regulation in the control of differentiation and energy metabolism of adipocytes by using Formaldehyde-Assisted Isolation of Regulatory Elements coupled with high throughput sequencing (FAIRE-seq) that detects regulatory elements in the genome.
- 8) The role of autonomic nerve system in the regulatory mechanisms of adipo-hepatic balancing.

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Department of Chronic Kidney Disease (CKD)

Associate Professor

Miki Nagase, M.D., Ph.D.

Associate

Shigetaka Yoshida, M.D., Ph.D.

Homepage <http://plaza.umin.ac.jp/~kid-endo/07-lab/18-nagaselab/nagaselabtop.html>

Introduction and Organization

The Department of Chronic Kidney Disease (CKD) was established in January 2009 by a donation from Japan Boehringer Ingelheim Co., Ltd., in cooperation with the Department of Nephrology and Endocrinology (Prof. Toshiro Fujita) and Department of Urology (Prof. Yukio Homma).

Chronic kidney disease (CKD) is a disease entity advocated by National Kidney Foundation in 2002. CKD is regarded as one of the highest priority medical issues at present. CKD patients, if untreated, will develop end-stage renal disease requiring artificial dialysis. They are also high risk group of cardiovascular disease (CVD).

The main research objects of this department are to elucidate the molecular mechanisms by which metabolic syndrome increases the risk of CKD or by which CKD promotes CVD, to identify novel therapeutic target molecules, and to develop new diagnostic and treatment strategies, and to construct experimental evidence that can be applied to the CKD treatment.

We cooperate with Department of Nephrology and Endocrinology, Department of Urology, and other research groups having abundant clinical resources and analytical strategies, and perform basic research as well as translational and clinical researches. We hope that our department will become the center of excellence for CKD research.

Research activities

In our department, we investigate the roles of aldosterone/mineralocorticoid receptor (MR) system, salt, adipokines, oxidative stress, inflammation caused by immune cells in the processes linking metabolic syndrome to CKD, especially focusing on glomerular podocyte injury, a major cause of proteinuria. Aldosterone has recently been recognized as an important mediator of target organ damage, in addition to its role in salt and blood pressure homeostasis. Recent epidemic of obesity and high salt diet in our modern society are postulated to cause inappropriate activation of the aldosterone/mineralocorticoid receptor (MR) system, leading to cardiovascular and renal disease. We demonstrated that metabolic syndrome rat is susceptible to renal injury, especially when fed a high salt diet, due to inappropriate aldosterone/MR activation. Adipocyte-derived aldosterone-releasing factors (ARF) may account for aldosterone excess in this model. We further identified small GTPase Rac1 as a novel activator of MR, and reported that the ligand-independent MR activation by Rac1 contributes to the nephropathy of several CKD models.

We have several ongoing projects, such as basic research focusing on “cross-talk between Rac1 and MR”, and translational research to verify the clinical significance of Rac1/MR activation and to develop epoch-making diagnostic and therapeutic strategies.

- (1) Analysis of Rac1-MR interaction and target organ injury, using experimental models of metabolic syndrome (KKAy, SHR/cp, diet- induced obesity, etc.). Search for stimuli causing Rac1 activation.
- (2) Generation of cell type-specific (ex. podocyte-specific) Rac1 Tg / KO mice.
- (3) Identification of ARF, based on the comparative analysis of fat cell conditioned media from obese SHR and non-obese SHR.
- (4) Elucidation of other mechanisms of MR activation.
- (5) Development of drugs (reagents to inhibit Rac1, ARF, and newly-identified target molecules), diagnostic tools (indicators of MR activation in the target organ), specification of clinical conditions in which Rac1-MR overactivation is involved.

Res. 2010 Jun;33(6):616-21.

Teaching activities

The education of post-graduate students is also an important task of our department. Our staffs help the students to plan and perform basic experiments and/or clinical studies, to make oral or poster presentation at Japanese or international society, and to publish scientific article. We have educational programs including journal club in order to polish their academic skills.

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Department of Molecular Structure and Dynamics

Project Professor

Nobutaka Hirokawa, M. D.

Project Associate

Tadayuki Ogawa, Ph. D.

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

Teaching activities

We are involved in teaching medical students and Master course and Ph.D course students in the following lectures and laboratory courses together with the Department of Cell Biology and Anatomy.

I.

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

II.

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

to medical students and students of other faculties.

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

Especially we devote ourselves for the teaching of the cutting edge approaches of new light microscopy such as the Photoactivated Localization Microscopy (PALM), cryo-electron microscopy and X-ray crystallography.

Research activities

Our laboratory studies molecular motors and rail

microtubules and the mechanisms of intracellular transport. To study these molecular mechanisms we use new molecular cell biological approaches including cutting edge light microscopies, cryo-electron microscopy of molecular resolution, X-ray crystallography, biophysics, molecular biology and molecular genetics. We aim to study the structure and dynamics of the molecular motors in vitro and in vivo at the highest spatial and temporal resolution and on these bases try to elucidate functions of molecular motors in vivo combining molecular genetics.

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Department of Continence Medicine

Professor

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

Research Associate

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 since July 1st 2010 to facilitate researches specially focusing on continence medicine. The aim of our department is to contribute to the advancement of continence medicine through basic and clinical researches on regulation mechanisms of lower urinary tract (LUT) function and pathophysiology of LUT dysfunction, as well as function/dysfunction of lower bowel and pelvic floor.

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

Clinical activities

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

Teaching activities

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

Research activities

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

1. To elucidate bladder sensory transduction mechanisms
2. To disclose pathophysiology of development of detrusor overactivity/OAB
3. To find useful biomarkers for IC/BPS
4. To evaluate the effects of metabolic syndrome on LUT function
5. To develop novel pharmacological treatment for refractory LUT dysfunction
6. To establish continence-care system consisted of multi-disciplinary professionals to contribute to the advancement of continence medicine

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Department of Medical Genomics

Professor

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

Associate Professor

Young Lim Choi, M.D., Ph.D.

Lecturer

Masahito Kawazu M.D., Ph.D.

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. It is, therefore, likely that therapeutic efficacy with current cytotoxic drugs is coming to their limit. To overcome such limitation, it should be desirable to develop effective targeted therapies against causative oncogenic molecules in each cancer.

Recently, Professor Mano and Associate Professor Choi has developed an efficient method to construct retroviral cDNA expression libraries even from a very small amount of clinical specimens. Application of such technology to a lung cancer specimen led to the discovery of a novel, fusion-type tyrosine kinase EML4-ALK. This discovery became the driving force to rapidly develop selective and efficient inhibitors against the catalytic activity of ALK and to conduct clinical trials for lung cancer patients with the inhibitors. This EML4-ALK story is clearly a “proof-of-principle” for the above hypothesis that, to obtain a major breakthrough in cancer treatments, we have to identify and develop drugs against essential growth drivers in cancer.

On the other hand, rapidly emerging new

generations of nucleotide sequencing-technologies have enabled to determine tens of gigabases of nucleotides in a single experiment. With the advent of such technologies we can now sequence an entire human genome in a relatively short period of time. Application of this approach to cancer specimens makes it possible to “resequence” cancer genomes and to identify mutated genes only in cancer genomes, which are the candidates for cancer-causing genes.

Under such circumstances, the Department of Medical Genomics was established in September, 2009 with the aim to identify essential growth drivers in every cancer, by taking advantage of our functional screening system coupled with the next generation sequencing technologies. The Department of Medical Genomics has been settled by the tight support from the Department of Molecular Pathology (Professor Kohei Miyazono) and by the donation from Astellas Pharma Inc. and Illumina, Inc. From April, 2010, Masahito Kawazu, M.D., Ph.D. newly joined our department as a Lecturer.

The Department of Medical Genomics enjoys a wide range of research collaboration with many academic institutes within Japan and also from abroad. Especially, the Department of Medical Genomics is under an intimate collaboration with Division of Functional Genomics, Institute of Molecular Medicine, Jichi Medical University, which is chaired by Professor Mano.

Teaching activities

We jointly take the responsibility for the lectures of “General Pathology” for the undergraduate students of the School of Medicine. Additionally, Professor Mano has conducted a number of seminars worldwide to propose the significant importance in cancer genomics.

Research activities

The Department of Medical Genomics tries to fulfill our goals mainly through the 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.

Expression of EML4-ALK in lung epithelial cells generated hundreds of adenocarcinoma nodules in both lungs of transgenic mice, and treatment of such mice with a selective inhibitor against the catalytic activity of ALK led to a rapid disappearance of such nodules from the mice (*PNAS* 105:19893). These results reinforce the essential role of *EML4-ALK* in the carcinogenesis of lung cancer patients positive for the

fusion gene, also prove that selective inhibitors against ALK should become effective therapies for lung cancer.

Indeed, most pharmaceutical companies are currently developing ALK inhibitors, and more than five of different inhibitors are under clinical trials to treat EML4-ALK-positive lung cancer, and the efficacy of one of such compound, crizotinib, has been published already. Surprisingly treatment with crizotinib resulted in ~90% of response rate plus the presence of patients under complete remission.

Currently, we are trying to apply our retroviral screening technologies to other cancer subtypes, and to discover novel oncogenes that could be efficiently targeted.

(2) Cancer genome resequencing

In addition to the functional screening shown above, we also tried to search for somatically mutated genes in human cancers. As an initial trial for this purpose, we developed an extra-large nucleotide sequencing array (Sequencing Wafer) with Perlegen, Inc. (Mountain View, CA, USA), which can determine ~nine millions of bases.

With such wafer, we analyzed the coding sequences of ~5600 protein-coding genes among the purified blasts of acute myeloid leukemia as well as paired normal T-cells (*Oncogene*, Epub ahead of print. DOI: 10.1038/onc.2010.117). Through such screening, we could identify a novel activating mutation in the JAK3 tyrosine kinase. Further screening of JAK3 mutations in another cohort of leukemia led to the discovery of various JAK3 mutations with a frequency of 3.14%. It is, therefore, likely that anomaly in JAK3 kinase is responsible for the transformation of a subset of acute myeloid leukemia.

In addition, the screening with the wafers also revealed a non-synonymous somatic mutation in *DNMT3A* that encodes one of the responsible methyltransferases for the *de novo* methylation in our genome. The mutated DNMT3A carries only <50% of its enzymatic activity compared to its normal counterpart, and was found in ~4% of our leukemia cohort. This was the first discovery of somatic mutations in DNMT genes in humans.

We have recently succeeded in developing a

resequencing technology with a high accuracy with the next generation sequencing system, "Genome Analyzer" from Illumina, Inc. Through this technology we are currently pursuing to discover other somatically mutated genes in human cancer specimens.

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Department of Molecular Psychiatry

Associate Professor

Kazuya Iwamoto, Ph.D.

Assistant Professor

Miki Bundo, Ph.D.

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Introduction and Organization

Major mental disorders such as schizophrenia, affective disorders, and developmental disorders are severe disorders showing high prevalence rate in every population. They not only bring long-lasting suffering to patients and their families, but also cause tremendous loss from an economical view. Surprisingly, cause of illness and pathophysiology of mental disorders remain largely unclear. The Department of Molecular Psychiatry has been established at the Graduate School of Medicine, University of Tokyo since February 1st 2010, by the donation from three pharmaceutical companies — *Astellas Pharma*, *Dainippon Sumitomo Pharma*, and *Yoshitomi Yakuhin*. The aim of this department is to contribute the understanding of cause of illness and pathophysiology of major mental disorders at the molecular level, through the close collaboration with *Department of Neuropsychiatry at the University of Tokyo*.

from *Department of Neuropsychiatry at the University of Tokyo* and postmortem brains provided from brain banks.

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Research activities

Specimen derived from mental disorders as well as animal models are examined by comprehensive approaches from genetic, molecular biological, cellular and behavioral point of views. Especially, we will focus on the study of blood samples provided

Endowed Department

(22nd Century Medical and Research Center)

Department of Clinical & Molecular Epidemiology

Project Associate Professor

Takanari Gotoda, M.D., Ph.D.

Project Associate

Takashi Yamamoto, Ph.D.

Homepage http://www.h.u-tokyo.ac.jp/research/center22/contribute/rinsyo_bunshi.html

Introduction and Organization

The Department of Clinical & Molecular Epidemiology was established in June 2004 as an endowed department (Mitsubishi Tanabe Pharma Co., Ltd.) of the Graduate School of Medicine, the University of Tokyo, under supervision of the Department of Nephrology and Endocrinology (Prof. Toshiro Fujita) of the University of Tokyo Hospital. At present, our department is also supported by the Pharmaceutical Department (Prof. Hiroshi Suzuki) and belongs to the 22nd Century Medical and Research Center, which partly represents the translational research activities of the University Hospital. At present, our research laboratory facilities are located at the 8th floor of the Central Clinical Service Bldg.2 and at the 10th floor of the Inpatients' Ward B of the University Hospital. Dr. Gotoda is entirely responsible for the management of the department, keeping close contact and cooperation with the other departments of the 22nd Century Medical and Research Center and with laboratories of the Department of Nephrology and Endocrinology and the Pharmaceutical Department, and focusing mainly on research activities.

Our department is established with the main aim of performing the clinical and epidemiological analysis on the metabolic syndrome in the Japanese population, of isolating susceptibility gene(s) to metabolic syndrome through molecular and genetic analysis on

human and rodent animal models, and of contributing to the development of novel diagnostic method and therapeutic agents for the prevention and treatment of the cardiovascular diseases. Above all, recently, we are focusing on the genetic susceptibility to visceral fat accumulation, a hallmark of the metabolic syndrome, and also on the genetic susceptibility to hypertension. Furthermore, we are also trying to elucidate the novel mechanistic action of the available pharmaceutical agents for the treatment of the metabolic syndrome such as the inhibitors of the renin-angiotensin system and the statins.

Clinical activities

Some of the members of our department is closely involved in clinical services related to both the out-patient and admission departments. We also attend clinical conferences and contribute to clinical activities of the Department of Nephrology and Endocrinology of the University Hospital, because our department is under supervision of the Nephrology and Endocrinology Department. We are also performing a translational research project using clinical materials derived from patients with agreement and approval of both the patients and the ethics committee of the University Hospital. Also, in cooperation with outpatient clinics and hospitals outside, we are collecting and analyzing the clinical data on metabolic syndrome from an epidemiological

standpoint with the aim of returning the fruitful results of the translational research to the clinical practice departments.

Teaching activities

Our department belongs to the Graduate School of Medicine and Faculty of Medicine, the University of Tokyo. We are constantly instructing several postgraduate students and supervising them in order to succeed in obtaining the medical doctor degrees of the University of Tokyo. We also contribute to examination of the applicants for the doctor degrees, and make several lectures for the students in the Faculty of Medicine at the University of Tokyo as well.

Research activities

Our research field of interest covers the followings.

- Identification and isolation of novel susceptible genes and related factors to metabolic syndrome through systemic molecular and biological analysis on human and rodent animal models of metabolic syndrome.
- Performance of clinical and epidemiological analysis with regard to metabolic syndrome.
- Development of novel diagnostic method for risk factors of cardiovascular diseases.
- Contribution to the development of preventive and therapeutic novel agents to treat patients with metabolic syndrome.
- Exploration of novel mechanisms of action of available pharmaceutical agents to treat patients with cardiovascular diseases.

First of all, with regard to analysis on metabolic syndrome, we analyzed clinical and epidemiological data in the Japanese population by means of factor analysis focusing on metabolic syndrome. The results indicated that, even in the Japanese population where severe insulin resistance can hardly be seen and common, the presence of insulin resistance is a crucial factor underlying the clustering of risk factors related to metabolic syndrome.

Recently, through the genetic analysis of animal model of metabolic syndrome, we have successfully isolated and identified a novel gene underlying

visceral fat accumulation, a hallmark of metabolic syndrome. Its characterization is described below in detail.

The spontaneously hypertensive rat (SHR) is an important genetic animal model of hypertension, dyslipidemia, and insulin resistance closely related to metabolic syndrome. We previously reported the genetic heterogeneity among SHR strains, most importantly, the fact that SHR strains could be divided into two separate groups according to the presence or absence of genetic null mutation at the CD36 gene. Representatively, the SHR/NCrj strain lacks CD36 due to the mutation while the SHR/Izm strain has normal CD36. Although these two strains are quite different in terms of visceral fat accumulation, insulin secretion capacity, kidney weight and proteinuria, very interestingly, these differences could not be ascribed to the CD36 gene mutation, indicating the presence of another important genetic abnormality. By performing the so-called QTL (quantitative trait locus) analysis on the F2 cross population between the two SHR strains, we have identified a QTL linked significantly to epididymal fat weights and blood pressure located near D1Wox28 on rat chromosome 1. Next, as the result of a systematic screening of genes located within the candidate QTL region by means of gene expression analysis with a Gene-chip microarray, we have identified the SLC22A18 gene located at the peak of the QTL region. Interestingly, SHR/NCrj has a point mutation at the donor splice site of an intron of the SLC22A18 gene, while SHR/Izm lacking the mutation found in SHR/Izm has wild-type SLC22A18. The SLC22A18 gene is most abundantly expressed in liver and kidney, and it is also expressed ubiquitously, for example, in the adipose tissue and pancreatic islet cells. While the physiological function of SLC22A18 remains largely unknown, it is postulated as a membranous protein that would be possibly involved in the membranous transport. It is also predicted that the donor splice site mutation found in SHR/NCrj should cause the skipping of a single exon encoding 34 amino acids that would be crucial for normal function of SLC22A18. In fact, the kinetic analysis using a radio-labeled chemical agent that is postulated to be an exogenous substrate for SLC22A18 on isolated adipocytes clearly demonstrated that the adipocytes derived from SHR/NCrj with the

SLC22A18 defect have significantly altered function in terms of uptake of the substrate into adipocytes as compared with those from SHR/Izm, establishing the functional significance of the mutation.

Based upon these observations, we hypothesized that the genetic and functional abnormality of SLC22A18 could cause visceral fat accumulation, kidney impairment, hypertension and impaired insulin secretion. To test this hypothesis, we have established cell lines that either overexpress or underexpress SLC22A18, and also overexpressed in vivo with use of adenovirus vectors. We are also trying to establish genetically-engineered mice such as transgenic mice overexpressing rat SLC22A18 and knockout mice deficient in the SLC22A18 gene. By analyzing the phenotypes of those genetically-engineered mice, we plan to explore the clue to the etiological mechanism of visceral fat accumulation. Interestingly, since the function of SLC22A18 can possibly be regulated by some synthetic exogenous substrate, verification of the above hypothesis may open a new way to develop a novel pharmaceutical agent to treat metabolic syndrome focusing on SLC22A18 as a new target.

As another important approach to metabolic syndrome, we have also generated knockout mice deficient in the gene for KAT-1 (kynurenine aminotransferase-1), which we previously identified a promising candidate gene of hypertension in SHR. Interestingly, those homozygous knockout mice developed hypertension and manifested insulin resistance, sympathetic hyperactivity, resistance to diet-induced obesity, and diabetic insipidus. These observations may serve to develop a novel pharmaceutical agent to treat metabolic syndrome focusing on KAT-1 as a new target as well.

Finally, we also carry out a series of research experiments aiming at exploration of novel mechanisms of action of available pharmaceutical agents to treat patients with cardiovascular diseases.

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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 really 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.

Clinical activities

We provide outpatient services for cancer patients. All interventions performed in the department are defined by the protocols of the particular clinical trial approved by the IRB. The following clinical trials are underway in our department:

Cancer vaccine

1. UMIN000001260, active, recruiting, IRB number: 1935-(2). A phase I study of vaccination with NY-ESO-1f peptide mixed with Picibanil; OK-432 and Montanide; ISA-51 in patients with cancers expressing NY-ESO-1 antigen
2. UMIN000001857, completed, IRB number : 2475. A phase I study of cancer vaccine with NY-ESO-1 overlapping peptides in patients with advanced cancers expressing NY-ESO-1 antigen. Condition: advanced esophageal cancer, stomach cancer, non-small cell lung cancer (NSCLC), malignant melanoma, bladder cancer.

Dendritic cell therapy

3. C000000451, terminated. Clinical study of intratumoral dendritic cell injection after radiofrequency ablation therapy in hepatitis C virus-related hepatocellular carcinoma patients
4. UMIN000000971, terminated, Clinical study of intratumoral dendritic cells (DC) injection after radiofrequency ablation (RFA) therapy for the treatment of hepatitis C virus-related hepatocellular carcinoma (HCC) patients
5. UMIN000002136 , active, recruiting, IRB number: 2492. Safety, efficacy and immunogenicity of autologous tumor lysate-pulsed dendritic cell therapy in patients with advanced renal cell carcinoma
6. UMIN000002837 , active, recruiting, IRB number: 2759. Safety, efficacy and immunogenicity of autologous tumor lysate-pulsed dendritic cell therapy after resection of stage2A (T2N0,T3N0) esophageal cancer

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

7. C000000336, active, recruiting, IRB number: 1290-(4). Clinical study on safety and efficacy of adoptive transfer of autologous gamma/delta T lymphocytes in patients with non-small cell lung cancer.
8. UMIN000000628, terminated, IRB number: 1511-(5). A study to evaluate the safety and efficacy of ex vivo expanded autologous gamma/delta T cell infusion following zoledronic acid sensitization in patients who received radiotherapy for bone metastases.

9. UMIN000000854, active, recruiting, IRB number: 1781-(1). Clinical study on efficacy and safety of autologous gamma/delta T cell transfer therapy after pulmonary metastasectomy of colorectal cancer
10. UMIN000001419, active, recruiting, IRB number: 2120-(1). The efficacy and safety of autologous gamma/delta T cell transfer therapy for esophageal cancer
11. UMIN000001418, terminated, IRB number: 2176-(1). The efficacy and safety of autologous gamma/delta T cell transfer therapy for extrahepatic metastasis of hepatocellular carcinoma

Adjuvant $\gamma\delta$ T cell therapy

12. UMIN000000931 , active, recruiting, IRB number: 1810-(1). Clinical study to investigate safety and efficacy on combination of gemcitabine and autologous gamma/delta T cell transfer therapy after resection of pancreatic cancer
13. UMIN000001417 , active recruiting, IRB number: 2177-(1). The efficacy and safety of autologous gamma/delta T cell transfer therapy after resection of intrahepatic cholangiocarcinoma
14. UMIN000002839, active, recruiting, IRB number: 2760. The efficacy and safety of autologous gamma/delta T cell transfer therapy after resection of stage2A (T2N0,T3N0) esophageal cancer
15. UMIN000004130, active, recruiting, IRB number: P201019-11Z. Autologous gamma/delta T cell therapy for gastric cancer with ascites.

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 of 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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Division of Total Renal Care Medicine

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The Division of Total Renal Care Medicine, sponsored by Terumo Corporation, was established in 2004. Our goal is to provide end-stage renal disease (ESRD) patients with a renal replacement therapy most suitable for their way of life. In order to achieve this, we are making an effort to make peritoneal dialysis (PD) more available for patients, in a country where for most patients hemodialysis is virtually the only choice. We are presently conducting the following projects; (1) Research on establishing optimum PD therapy, (2) Educational courses for medical practitioners, and (3) research on improving clinical skills.

We are providing care for approximately 80 PD outpatients in our hospital with the support of the division of Nephrology and Endocrinology. All the 3 projects mentioned above are in close association with daily clinical practice. Our activities in 2010 were as follows:

(1) Research on establishing optimum PD therapy.

At the present state, the main cause of PD technique failure is deterioration of peritoneal function due to long-term use of bio-incompatible dialysate. Biocompatible dialysates have been available since 2001, and our research is focused on peritoneal pathology after long-term use of new biocompatible PD fluids. We have reported the results in the

Peritoneal Dialysis International (in press). In addition, we have started the project of developing non-invasive methodology of diagnosing peritoneal membrane with the collaboration between medical-engineering institutions.

(2) Educational courses for medical practitioners.

With the help of many nephrologists and nurses in our hospital, we have trained 27 nephrologists and 41 renal nurses from 25 facilities (either university hospital or central hospital in their area) from 15 prefectures in Japan in 2010. To date, we have trained 156 nephrologists and 101 renal nurses from 132 facilities between 2006-2010.

(3) Research on improving clinical skills.

PD is a mode of therapy in which the patient greatly participates in treating his own disease. Therefore, the patient needs to face up to his own disease, and to know how to acquire the skills needed for self-management. Based on this standpoint, we have felt that it is necessary to work with experts of other disciplines, such as the humanities. Thus, we have started some collaborative research with philosophers, sociologists, and cognitive behavioral therapists.

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Department of Integrated Molecular Science on Metabolic Diseases

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Introduction and Organization

The Department of Integrated Molecular Science 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.

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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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Introduction of this chair

We investigate the clinical usefulness and basic mechanisms of KAATSU training for rehabilitation in patients with various diseases. Especially, the KAATSU training is applied for muscle training in patients with cardiovascular, orthostatic dysregulation (OD) and respiratory (COPD) diseases. In addition, we have examined the clinical benefits of KAATSU training on cardiac rehabilitation. The KAATSU training also may be able to be applied to various kinds of fields such as the muscle training for astronauts, and severe patients with marked muscle atrophy in long-term bed rest.

Contents of our study

The KAATSU training is a unique technique of performing low-load exercises such as resistance exercises and treadmill with restricted muscle blood flow that results in an increase of muscle mass and muscular strength comparable to high-intensity training. Additionally, the KAATSU trainings can promote endocrine activities such as growth hormone (GH) secretion. Therefore, KAATSU training may be an epoch-making rehabilitation training for patients

with various kinds of diseases and old-aged patients. Also, since KAATSU femoral blood flow restriction induces the retention of blood flow in lower extremities, it reduces venous return, and induces subsequent hemodynamic changes like lower body negative pressure (LBNP). Thus, KAATSU may partly provide an orthostatic stimulus, and an effective countermeasure for cardiovascular deconditioning in weightlessness like LBNP. In our laboratory, we have been studying the clinical usefulness of the KAATSU training and comparing it with the ordinary rehabilitation. The main targets of our study are as follows: (1) Clinical usefulness of the KAATSU training in cardiac rehabilitation. There are many severe patients with muscle atrophy, especially in intensive care units (ICU) and high-intensive care unit (HCU), and in our cardiovascular ward. We have examined the possibility of KAATSU training for muscle training and early ambulation of these patients. (2) Clinical usefulness of this training in patients with respiratory diseases (COPD). There are several mechanisms involving the effects of KAATSU training including hypoxic effects of skeletal muscles, GH responses, and shear stress to cardiovascular hemodynamics. Therefore, we have also examined the basic experimental studies using a variety of methods

using electrophysiology and molecular physiology techniques. Also, we have investigated the effects of this rehabilitation on endothelial function by using PWV, ABI, and body plethysmography, and measurements of blood biomarkers such as endothelial progenitor cell and high sensitive CRP. We have started the cardiac rehabilitation program using KAATSU resistance training in outpatients with cardiovascular diseases. Finally, the KAATSU training may be applied to other clinical fields such as orthopedics and patients with endocrine diseases such as metabolic syndrome and diabetes mellitus. We hope that the KAATSU training can be accepted as a method of new advanced medical technology.

Further studies

We investigate the usefulness and basic mechanisms of KAATSU training in patients with various kinds of diseases. And, we believe that KAATSU training can provide a clinical benefit to a variety of fields for muscle training or muscle strength, and contributes to improve quality of life in patients including old persons.

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Introduction and Organization

Our department was open in January 2005, contributed by Hitachi, Ltd. and Hitachi Medical Corporation. Since then, the construction of clinical information database has been performed in collaboration with the Department of Cardiovascular Medicine of this University (Professor and Chairman; Dr. Ryozi Nagai). From 2008 to 2010, our research activities were supported by Theravalues Corporation and Hitachi, Ltd. In January 2011, new mission started under the contribution of DVx Inc., WIN INTERNATIONAL CO.,LTD. and Mitsubishi Tanabe Pharma. The aim of our department is to improve the clinical information database to the better one and put that into practical use in developing the clinical research.

Our department belongs to the 22nd century medical center in the University of Tokyo Hospital, which was founded as the front line of university-industry partnerships. As our research foothold is located in the hospital, we could keep the close connection with the bedside. Our department is thought to be suited for obtaining the maximum output in clinical research.

Research activities

The onset and progression of the disease are thought

to be caused by the environmental and/or genetic factors. What is the best way to identify the pathogenesis and the factors predicting the prognosis? The answer should be the filing of the clinical information.

We are constructing the effective framework to make the relevant clinical data available for research and performing the investigation to resolve the clinical questions, followed by the translation of its fruits to the bedside.

Another mission is to confer the explicit scientific re-evaluation on the health issues (e.g. eating habits, exercise, lifestyle) which have been believed to be empirically effective. This mission has to be followed by the prompt publicity of the “accurate” data led by our re-evaluation.

The realization of these missions above could be completed in a close collaboration with the academic groups and private enterprises. In this regard, we are ready to discuss and think together with anybody anytime.

In summary, our research field covers the issues as follows;

1. Development of information analysis system and systematization of clinical information
2. Clinical and/or genomic research utilizing the clinical information analysis system
3. Scientific verification of eating habits, exercise

and lifestyle

4. Analysis on the current state of the medical system
5. Spread of accurate medical information to society utilizing the information technology

Research Grants

A Grant from the Ministry of Health, Labour and Welfare (2008-2010) (to Morita H and Kohro T)

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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 department of Orthopaedic Surgery. 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 musculoskeletal diseases, including OA and OP. However, few prospective, longitudinal studies have been undertaken, 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 difficult to design rational clinical and public health approaches for the diagnosis, evaluation, and prevention of OA and OP without such epidemiological data.

We therefore established a large-scale nationwide osteoarthritis/osteoporosis cohort study called ROAD

(Research on Osteoarthritis 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 and second comprehensive clinic visit after a follow-up period of 3 years.

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Introduction and Organization

The Department of Health Management and Policy is an endowed department affiliated with the “22nd Century Medical and Research Center,” which is a new center of industry-academia collaboration established by the University of Tokyo Hospital. With donations from Nissay Information Technology Co., Ltd., the Department launched its first courses on April 1, 2005. The cooperative department is the Department of Medical Informatics and Economics, Division of Social Medicine, Graduate School of Medicine, University of Tokyo.

The objective of the Department’s activities is to promote interdisciplinary research designed to improve the quality and efficiency of systems related to health, medicine and nursing care. The mission of our research activities is as follows:

- 1) Conduct research on evidence-based health management and policy
 - 2) Bring the fruits of our research to society
- Our strategies for fulfilling this mission are as follows:
- 1) Develop and utilize a national database of Japan’s Diagnosis Procedure Combination (DPC)
 - 2) Collaborate with outside researchers in each research project

Research Activities

- (1) Research activities of the DPC Research Team

Over the past three years, the Department has participated in the DPC Research Team at the Ministry of Health, Labour and Welfare. In addition to providing support for the processing and analysis of DPC data, we have announced the results of these efforts. Since 2007, we have been preparing a system using the Department’s server to manage a database accumulated by the DPC Research Team, which contains about 3 million discharged cases every year.

(2) Other research activities

We have also put the following research into practice.

- (a) Research into cases of large-scale health hazards, such as drug-induced sufferings
- (b) Research into the existence of, and chief causes for, regional and departmental disparities in the supply of doctors
- (c) Research into the links between the volume and outcomes of surgical operations
- (d) Research into government regulations and the disparity between domestic and overseas prices of medical equipment
- (e) Research into the economic evaluation of healthcare services
- (f) Research into risk communication in food hygiene
- (g) Research into the policy evaluation of occupational health, such as measures to prevent karoshi (death from overwork)

- (h) Research on systems that contribute to medical safety
- (i) Research for the sustainable development of regional healthcare systems
- (j) Research on nationwide public-access defibrillators and improvement of outcomes after out-of-hospital cardiac arrests

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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 two project associate professors and three project research associates, along with a medical staff of approximately 40 employees in the health-screening center.

Clinical Activities

CDRPM is responsible for the clinical activities in the CDRPM Health Screening Center. In this 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) systems, ultrasound imaging systems, 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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Department of Hospital Environment

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※For this department, this year's text is the same as that published last year.

Introduction and Organization

Department of Hospital Environment was founded on July 1, 2005, when the surgical center of Tokyo University Hospital celebrated its 50th year anniversary. Its aim is to improve the hospital management and environment on the basis of the peri-operative medicine and management of operating rooms (OR's).

This department is considered one of the few laboratories, in which these researches are performed integrally in Japan.

Clinical activities

Prevention of health care associated infection is mandatory so that the high quality of healthcare service is provided to all patients. Moreover, it is known that healthcare associated infection is one of the main causes to increase the expenditures of healthcare services. For instance, it is required to prevent healthcare associated infections perioperatively in the infection control. For these reasons, the department of hospital environment is concerned with the management of operating theatres integrally.

Teaching activities

Handwashing is one of the most important procedures in the prevention of health-care associated infection. Surgical scrubbing is taught to the second grade

medical students February to March when they start their study in the clinical wards. Surgical scrubbing is also taught to the new residents of our hospital at the end of March and in the beginning of April.

Research activities

Current research topics are focused on the inactivation of prions, application of chlorine dioxide and ozone in the disposal of hospital sewage, and application of stereolithography to manufacture the reduced-scale models of OR's.

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Department of Clinical Motor System Medicine

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Introduction and Organization

The department of Clinical Motor System Medicine was established in 22nd Century Medical and Research Center in 2005, which is an endowment department supported by Eisai Co., Ltd. and in close collaboration with department of Orthopaedic Surgery. Our department has been established for the study of locomotor system medicine.

Research activities

Our research field covers observational and genomic epidemiology and main target diseases are osteoarthritis, spondylosis and osteoporosis. Osteoarthritis and osteoporosis are major public health issues in the elderly that cause impairment of ADL/QOL. The number of patients with these diseases is rapidly increasing in Japan, however, few epidemiologic indices have been established and there is an urgent need for a comprehensive and evidence-based prevention strategy. We set up a large-scale nationwide osteoarthritis/osteoporosis cohort study called ROAD (Research on Osteoarthritis/osteoporosis Against Disability) in 2005 for the pursue of genomic and etiological evidence. We have to date created a baseline database with detailed clinical and genomic information on three population-based cohorts with total 3,040 participants in urban, mountainous and seacoast communities of Japan. Recruitment and baseline visits began in

October 2005 and were completed over a 1.5-year period, with the last visit in March 2007. A second comprehensive clinic visit is scheduled for October 2008 after a follow-up period of 3 years.

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Introduction and Organization

The Department of Health Care Safety Management was established in the 22nd century medical center of the University of Tokyo Hospital by the contribution of Tokio Marine & Nichido Fire Insurance Co., Ltd. in December, 2005.

The public concern to the malpractice and the medical affairs dispute has risen in developed countries with several events such as the public inquiry into children's heart surgery at the Bristol Royal Infirmary and the accidental chemotherapy overdoses occurred in the Dana-Farber Cancer Institute at the end of the 20th century. Reports of media in our country concerning the malpractice and the medical affairs dispute increase suddenly on the boundary of 1999. Fears rise to making the criminal case through the mandatory reporting to the police by the Medical Practitioners Law Article 21. Some events become targets of investigations while several verdicts are put out as acquittals. There exist various discussions and confusions over the intervention of the police authority procedures to the process of medical treatment.

On the other hand, in the medical affairs dispute over the civil affairs compensation for damages, a lot of

cases have been done through various channels such as the correspondence procedures of the explanation and the reconciliation before they become lawsuits. In spite of such an effort, the civil affairs health care lawsuit number has kept increasing from 1970s (about 100 new cases received per year) to 2004 (1110 new cases per year), by the pace that doubled every ten years. Though the civil affairs health care lawsuit number shows a decreasing tendency after 2004, a lot of medical treatment disputes became lawsuits in 2009, 733 new cases received and 952 cases paid-up.

In our department, while looking straight at the reality of the malpractice and the medical affairs dispute from each aspect of the patient, the health care provider, and the society, it aims at a healthy rebuilding of the health care and the recovery of confidence to the medical treatment, by thinking about the ideal way of a better legal system in cooperation with the clinical site. With the best use of the experience in the state-of-the-art university hospital, we are establishing an approach that promotes mutual understanding by the conversation between the patient and the health care provider.

Research activities

Malpractice events during recent years have been frequently reported, and medical treatment disputes have become social problems. In this situation, basic researches concerning both the prevention of malpractice and the truthful resolution of medical accidents by preventing disputes and lawsuits are urgent issues. Such research activities are vigorously carried out in our department to return the result widely to the 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. Furthermore, as an educational extension, we also target medical staff for the purpose of training high-level professionals. In order to advance these educational extension activities, the development of various types of educational programs and teaching materials is also being carried out.

* Patient Safety Support Center Comprehensive Support Project

Training and related activities are carried out 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).

* Model Project for the Investigation and Analysis of Medical Practice-Associated Deaths

As part of this project, our training targets the concerned model project personnel, hospital patient safety managers, and related staff.

Clinical activities

Based on the research results described above, this department supports the operation of the “Patient Consultation - Clinical Ethics Center” newly established at the University of Tokyo Hospital. Together with on-site supporting measures, we promote research related to topics transmitted from

the site and education for staff of the site.

References

Research Article

1. Shiho Andoh, Tomoko Takahashi, Maiko Mizuki, Kenji Harada, Yasushi Kodama. Current status of the medical safety support center in Japan. The Japanese Journal of Quality and Safety in Healthcare. 2010;5(4):296-305 (in Japanese)

Review Articles

1. Yasushi Kodama. Risk management for emergency outpatient's care. Separate volume of ER magazine. 2010;7(2):152-162 (in Japanese)
2. Yasushi Kodama. Looking back on ten years for patient safety and medical affairs dispute. ICU and CCU. 2010;34(10):870-876 (in Japanese)

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Conference Presentations

International Meetings

1. Shiho Andoh. Analysis of medical complaints and consultations at patient safety support centers in Japan. 2010 NPSF Annual Patient Safety Congress. 18-19 May 2010.
2. Shiho Andoh, Kenji Harada, Yasushi Kodama. Relationship among civil litigation, negligence, complaint, adverse event and medical practice-associated death in Japan. 8th Australasian Conference on Safety and Quality in Health Care. 6-8 September 2010.

Domestic Meetings

1. Yasushi Kodama. Expectation for Japanese healthcare safety investigation mechanism. Japanese Surgical Society 110th annual scientific meeting.
2. Yasushi Kodama. Thinking about the next ten years for the view of healthcare safety and dispute. Japanese Pediatric Society 113th annual scientific meeting.
3. Yasushi Kodama. Healthcare safety and dispute. Japanese Orthopaedic Association 83rd annual scientific meeting.
4. Yasushi Kodama. Can a human error be judged? Can the life be defended by the penalty? Japanese Society for Quality and Safety in Healthcare 5th annual scientific meeting.
5. Yasushi Kodama. Healthcare and the law. 5th Annual Congress of Japanese Society for Quality and Safety in Healthcare.
6. Kenji Harada. Akira Akabayashi, Sadayuki Takimoto, Susumu Nakajima, Yasushi Kodama. Guideline decision of "Range where informed consent acquisition by document is necessary"

based on congressional questionnaire survey. 5th Annual Congress of Japanese Society for Quality and Safety in Healthcare.

7. Shiho Andoh, Tomoko Takahashi, Maiko Mizuki, Kenji Harada, Yasushi Kodama. Investigation report concerning current state of management of patient safety support centers. 5th Annual Congress of Japanese Society for Quality and Safety in Healthcare.
8. Shiho Andoh, Mayumi Yoshimura, Akiko Kuniyoshi, Nana Tanaka, Tomoko Takahashi, Maiko Mizuki, Kenji Harada, Yasushi Kodama. Making of consultation guidebook 2009 for patient safety support center staff. 5th Annual Congress of Japanese Society for Quality and Safety in Healthcare.
9. Tomoko Takahashi, Shiho Andoh, Maiko Mizuki, Kenji Harada, Yasushi Kodama. Execution report of training association and delivery course intended for patient, resident, and medical institution by using education and the enlightenment slide 'To become a wise patient.' 5th Annual Congress of Japanese Society for Quality and Safety in Healthcare.

Division of Molecular Cardiovascular Metabolism (Daiichi-Sankyo Company, Limited)

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Introduction and Organization

In order to investigate common diseases such as hypertension and their reno-cardiovascular complication, which is induced by defluctive lifestyle (salt excess, obesity, and so on), the Division of Molecular Cardiovascular Metabolism was started with donation of Daiichi-Sankyo Company Limited and supported by the Department of Nephrology and Endocrinology, in April 1, 2006. This division consists of the above-mentioned two staffs and a few part-time staff and graduate fellows. Our academic activity is majorly basic research using animals. However, we also participate in clinical research.

Teaching activities

In March of 2007, 2008, and 2010, total three graduate fellows took the medical degree. And now a few graduate fellows work in our laboratory.

Research activities

Basic Research: We are investigating the role of reactive oxygen species (ROS), the sympathetic nervous system, and the renin-angiotensin-aldosterone system (RAAS) in the pathophysiology of salt-sensitive hypertension, metabolic syndrome, and

their reno-cardiovascular complication.

For example, we demonstrated that sympathoexcitation by oxidative stress in the brain mediated blood pressure (BP) elevation in salt-sensitive hypertension and that obesity-induced hypertension. Actually, high fat intake and salt excess synergistically increase BP and progress organ damage. Recently, our data suggest that the similar central mechanism contributes to increase in BP and progression of renal damage in chronic kidney disease. This finding suggests that sympathoexcitation by ROS in the brain is a common and important mechanism for pathophysiology of many types of hypertensive disease. Recently, we elucidated the role of brain aldosterone in ROS-induced central sympathoactivation in these types of hypertension. In addition, we suggested that sympathoactivation contribute to glomerular injury in chronic kidney disease models using glomerulus-specific delivery system of tyrosine hydroxylase siRNA.

Also, we demonstrated that prepubertal salt loading caused more severe hypertension and renal injury compared with high salt intake in adulthood probably due to mineralocorticoid receptor (MR) activation, inflammatory and oxidant action, and α_1 -adrenoceptor activation (6). This investigation may clarify the pathophysiology of defluctive lifestyle-induced hypertension and renal damage in prepubertal age.

In addition, we suggested that MR activation also contribute to the development of inflammation-induced renal injury, such as lupus nephritis. We are further examining the role of MR in lupus nephritis.

Clinical investigation: Now, we are doing coordinating and secretarial work of a few clinical trials in the Department of Nephrology and Endocrinology, and join as a steering committee of clinical trial of the other institute.

We are investigation a common disease such as hypertension and metabolic syndrome, and can indicate meaningful results.

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Introduction and Organization

The Department of Healthcare Quality Assessment (HQA) was established in 2006 and performs researches on healthcare quality improvement in collaboration with the Department of Cardiothoracic Surgery in University of Tokyo. HQA has collaborated with the Department of Health Economics and Epidemiology Research from 2009 and with the Department of Pediatric Surgery from 2010.

Health care reform should be focus on improving health and health care value for patients. As improving the value of health care is something only medical teams can do, HQA has collaborated with healthcare professional committees. HQA supports systematic data collection, data management, practical analysis and useful feedback. Our benchmarking projects based on clinical database and will drive quality improvement in each field. With such positive-sum competition, patients will receive better care, physicians will be rewarded for excellence, and costs will be contained. Three principles should guide this change: (a) the goal is value for patients, (b) medical practice should be organized around medical conditions and care cycles, and (c) results — risk-adjusted outcomes and costs — must be measured.

HQA already developed risk models and provide several practical tools for medical staff through joint research with Japan Cardiovascular Surgery Database (JCVSD). One of practical tools is JapanSCORE which allows a user to calculate a patient's risk of mortality and other morbidities. JapanSCORE incorporates JCVSD risk models that are designed to serve as statistical tools to account for the impact of patient risk factors on operative mortality and morbidity. HQA also conducted policy analysis and clinical researches which might contribute to healthcare quality improvement. Value-based competition on results provides a path for reform that recognizes the role of healthcare professionals at the heart of the system.

Research activities

For healthcare quality improvement, a) healthcare quality must be identified and b) quality indicators must be set and monitored in each healthcare region. A well-designed database system that collects clinical data continuously in reliable and validated manners is needed to identify healthcare quality, monitor quality indicators, and improve the quality of healthcare services. HQA has designed and managed nationwide database systems in collaboration with the Japan

Surgical Society, the Japanese Society for Cardiovascular Surgery and the Japanese Society of Gastroenterological Surgery.

Severity-adjusted indicators must be used for investigating clinical outcomes and exploring the systems providing the best practices to patients. HQA developed risk models and conducts outcome analyses based on systematic data collection. These analyses enable risk assessment and prognosis prediction of cardiovascular surgeries and benchmarking of the database-participating facilities. This information is useful for discussion in pre-surgery conference, patients' better understanding of treatment and promotion of healthcare quality improvement.

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Presentation

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Introduction and Organization

The Department of Anti-Aging Medicine was established at the 22nd Century Medical and Research Center of University of Tokyo Hospital in 2006. This department has a close relationship with the Department of Geriatric Medicine at the Graduate School of Medicine, University of Tokyo. The goal of this research program is to understand the genetic and environmental factors that contribute to the pathogenesis of age-related disorders, including obesity, diabetes, metabolic disorders, osteoporosis, osteoarthritis, sarcopenia, atherosclerosis, dementia, age-related macular degeneration, prostate cancer, mammary carcinoma, and immunocompromised conditions. In particular, the program aims to clarify the roles of sex hormones estrogen and androgen in normal, aging and disease processes. Through basic biomedical research, our department will reveal age-dependent changes at cellular, tissue, and whole-body levels, and will contribute to the development of molecule-targeted treatment and alternative prevention of age-related processes and diseases.

Research activities

Aging causes degeneration and dysfunction of cells in various organs, leading to the development of multiple disorders in elderly people, as exemplified by obesity,

glucose intolerance, dyslipidemia. Osteoporosis and osteoarthritis are also common bone and cartilage disorders among elderly people. In addition, aging is an important risk factor for the prognosis of hormone-dependent tumors, prostate cancer and mammary carcinoma. Since aging and age-related disorders affect the quality of daily living and lifespan of elderly people, we will identify the genetic and environmental factors that control aging processes using recent technology of human genetics and molecular biology.

Our recent findings contribute to the progress in three following research fields.

1. We originally identified estrogen-responsive finger protein (Efp/TRIM25) as an estrogen target gene through genome binding-site cloning technique. Efp has a structure of the TRIM/RBCC protein, with RING finger, B-box, and coiled-coil domains, and it has been shown as a critical molecule that promotes the progression of mammary carcinoma. In addition we recently discovered that Efp has another important role in antiviral defenses. Extending our findings on TRIM25, we also study the functions of other TRIM proteins in normal states and in cancer and immune response, including TRIM5 α , TRIM17 (Terf), TRIM44 and TRIM63.
2. Using chromatin immunoprecipitation microarray

analysis and systems biology approach, we discovered novel androgen responsive genes including UGT1A1, CDH2, APP, and FOXP1. The tumor-promoting effect of APP has been shown in *in vivo* models of prostate cancer.

3. As a genetic approach, we perform single nucleotide polymorphisms (SNP) analysis to identify disease-related factors for osteoporosis, osteoarthritis, and age-related macular degeneration. Through genome-wide associated study and candidate gene approach, we identify several interesting disease-related genes and focus on the functional studies for these genes. We also combine mouse genetics to solve the functions of disease-related genes in physiological states as well as in pathophysiological states.

Our intensive studies will provide novel molecular evidences for aging processes, which will be useful for the establishment of anti-aging medicine and the development of novel therapeutic modalities for age-related disorders.

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※For this department, this year's text is the same as that published last year.

Introduction and Organization

The recent advent of various medical imaging modalities including high-field magnetic resonance imaging, multi-detector row computed tomography, computed radiography, ultrasonography, and endoscopy enables us to obtain data with high spatial and temporal resolution. However, the interpretation of large amounts of volumetric data places a burden on radiologists.

We operate a dedicated image server to systematically develop the methods of extraction, analysis, storage, and integration of clinically valuable information contained within medical image data, introducing a state-of-the-art engineering technology and recent evidence obtained by cognitive science. We aim to apply our results to public health service, teleradiology, professional education, and high-potential expert system that can assist diagnostic radiologists.

Research Activities

Our present research includes the following:

1. Image processing to provide comprehensive 3D-display
2. Computer-aided detection and diagnosis in upper abdomen
3. Data-mining from medical image databases

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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
 - 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 Department of Clinical and Genetic Informatics and the Department of Clinical Epidemiology and Systems
 - Consultation works on medical statistics and research methodology
 - Data center is working at our department and staffs are included as a biostatistician or a clinical data manager

Research activities

In addition to activities described above, we are

developing common tool for clinical research such as Standardized Operating Procedures (SOPs) in conducting clinical research.

Research on Clinical Data Interchange Standards Consortium (CDISC) in collaboration with University Hospital Medical Information Network (UMIN) is actively ongoing. The mission of CDISC is to develop and support global, platform-independent data standards that enable information system interoperability to improve medical research and related areas of healthcare and we are challenging to convert several academic clinical trial data to CDISC Standards formats.

Finally, we started the Eplerenone Combination Versus Conventional Agents to Lower Blood Pressure on Urinary Antialbuminuric Treatment Effect Trial (EVALUATE) in collaboration with the Department of Nephrology and Endocrinology, Department of Pharmacoepidemiology, University of Tokyo Clinical Research Center and UMIN. The responsibility of the Data Center is the data management including operation of the internet system of the patient registry and informing data and of handling the individual case safety reports for the serious adverse events. Also we are responsible for Biostatistics / Data management Division of The Clinical Research Support Center in University of Tokyo Hospital.

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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 quantitative pharmacology, system 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 (Astellas Pharma Inc, Eisai Co Ltd, Shionogi & Co Ltd, Daiichi Sanko Co Ltd, Takeda Pharma Co Ltd, Novartis Pharma K K, and Banyu Pharma Co Ltd).

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 under-graduates 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 Prof. Sugiyama in 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.

Evaluation and prediction of absorption and metabolism in the gut

Oral drugs need to be absorbed from the gastrointestinal tracts in order to exert therapeutic effects. In reality, therapeutic potential of many drugs are unstable or reduced due to low absorbability and/or extensive metabolism in the gut. Since multiple issues are concerned in the absorption process of a drug, its modeling and simulation have been met with limited success. We developed a new and reliable evaluation method of the intestinal metabolism. And furthermore, a new PK model was constructed for consideration of physiological intestinal absorption and metabolism.

Study on ethnic difference in pharmacokinetics

Nowadays, a new drug development is conducted internationally in general, and hence, clinical studies are quite often performed first in overseas and then introduced in Japan. Therefore, evaluation of ethnic difference is very important for the success of new drug development in Japan.

We surveyed and analyzed ethnic differences in PK systematically, and found that ethnic differences observed in phase 1 study in Japanese subjects are often unreliable since inter-study difference is apparent. On the other hand, it was revealed that a degree of ethnic difference in PK is rather small compared with obvious inter-individual difference. From the results of this study, it would be needed to reconsider the role of phase 1 studies conducted in Japan. Furthermore, it may be helpful for consideration of strategies for new drug development in Asian countries in the future.

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International Meetings

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4. Sasaki Y, Hisaka A, Suzuki H. Development of Population Model for Expression of Cytochrome P450s and Relating Enzymes in Human Liver Microsome. 18th International Symposium on Microsomes and Drug Oxidations, Beijing, China, May 16-20, 2010.

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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 (Professor Shinichi Takamoto) and the Department of Cardiology (Professor Ryoza Nagai) 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 transplantation, ventricular assist device, and regenerative therapy. The Department is also supported by thirteen companies,

Clinical Activities

1. Heart Transplantation (HTx)

Patients who performed heart transplantation in our hospital (15 patients) or in abroad transferred from our hospital (8 patients) 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. The Organ Transplant Law was revised in July 2010, the number of brain death cadaver increased dramatically from August 2010, Between August and December 2010 6 patients were performed heart transplantation in the University of Tokyo Hospital.

2. Ventricular Assist Device (VAD) Therapy

58 patients were treated with Ventricular assist device (VAD) since November 2002 when the University of Tokyo Hospital started heart transplantation program. 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. 19 patients were treated with VAD, 16 were treated in Hospital ward and 3 were treated in the outpatient clinic.

VAD was implanted in 6 patients in 2010 among them Toyobo paracorporeal VAD were implanted in 5 and HeartMate II was implanted in one patient. They were registered to JOTN (Japanese Organ Transplant Network) are waiting for HTx.. We assisted VAD implantation in seven patients in affiliate or cooperative hospital in 2010 to establish VAD network in Kanto Shinsyu and Tohoku prefectures.

3. Compact CP (external counter-pulsation)

Compact CP is a system of external counter-pulsation circulatory support system, which has been developed with collaboration of Nishimura Co. Ltd. and the University of Tokyo Hospital. Compact CP therapy was performed in collaboration with on 10 patients at ICU for postcardiotomy cardiac failure and on 1 patient in out-patient clinic for unstable angina after CABG and PCI.

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 4 series of clinical trial of implantable rotary blood pump LVAD, EVAHEART, DuraHeart, Jarvik 2000, and HeartMate II since 2007.

EVAHEART, DuraHeart approved last December and insurance reimbursement was obtained this April. Other two LVAD will be approved within this year.

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Introduction and Organization

Our mission is to promote research and development of a novel integration system where pieces of patients' healthcare information are virtually combined together that are stored separately in diverse medical/healthcare facilities. Recently developed mobile information communication technologies in conjunction with cloud computing provide sturdy environment to build a "virtual ubiquitous health information space". We particularly focus on better clinical outcomes, as well as efficacy, safety, and security matters achieved by those innovative systems in the various medical/healthcare fields.

Research activities

To date we have been working on specific topics shown below since this lab was established in 2009. Our products have reached a stage of clinical validation, respectively. Furthermore, we are promoting collaborative research with several laboratories both inside and outside the campus, seeking for frontier fields of interdisciplinary research and practical medicine/healthcare fields. Through development of those specific products, we further aim to establish a systematic methodology for creating solutions for virtual ubiquitous health information space.

1. A 12-lead ECG system based on cloud computing for emergency care

Treatment of cardiovascular diseases inside medical facilities have improved dramatically in recent years. On the other hand, the outcomes of acute cardiovascular disease is not yet sufficient depending upon the local medical environment. In order to fill up those "gaps" between inside and outside the medical facilities, we working on creating a novel ECG system as a clinically valid approach to this problem. We have developed a cloud computing system with wirelessly transmission ECG units, potentially clinical usefulness due to the cloud-based server built. Deliverables of this study demonstrate that the application will be tested in several clinical fields FY2011.

2. Dialbetics: A novel smartphone-based self-management support system for type 2 diabetic patients

It is fundamentally important for diabetic patients to maintain appropriate balance of diet and exercise, although the clear solution for it has not yet been established. We have developed a novel smartphone-based self-management support system for type 2 diabetic patients. This new system has an automatic function of stratifying daily patient's biometric information such as blood glucose, blood pressure, and food intake retrieved by the home sensor and router according to medical risk evaluation.

Stratification engine feedback the risk level and raw data to the patients, as well as to the administrator only if the risk level indicates extremely high so that he/she can urge the patient to see or consult his health professionals as soon as possible. It has long been pointed out that introduction of telemedicine can problematically increase the burden of healthcare workers, even if its efficacy may be ascertained, suggesting the difficulties to maintain and promote the system. We are also struggling to develop a new system to overcome this kind of apprehension by developing a new algorithm to reduce the burden of health care workers. At present we performed series of pilot studies for about 10 people in accordance with the reviewed protocol of the ethics committee. We are to conduct 100-scale clinical trial to further confirm validation, efficacy and safety aspects of Dialbetics in FY2011. Besides we promote the evolutionary algorithm in collaboration with a specific research laboratory in Faculty of Engineering.

3. Integrated System on Smartphone for Medicine Taking Support to maintain adherence to medication

In clinical settings, adherence to medication is a potentially important issue, previously managed by maintaining its objective methodology has not been reliably established. We have sought a solution by mobile ICT, which deals with prescribing information from the hospital as well as dispensing information from a pharmacy, and centralizes the medicine-taking information obtained through wireless sensing unit equipped in the pill cabinet and a newly developed integrated application. This enables us to share information about patients' adherence to medication among healthcare providers and patients.

4. Advanced smartphone-based guidance system for outpatients

In order to improve convenience and amenity of university hospital outpatient services, we have developed a new guidance system on cell phones. This system will provide advanced function for reception from outside, reducing waiting time, fast-forward of prescription data to pharmacies, and so on. It will be tested in the outpatient department of the University of Tokyo Hospital in FY2011.

5. Various assistance applications on smartphone for medical/comedical personnel in hospitals

We have launched several development projects of mobile ICT systems to assist medical staff and medical technicians in the hospital.

3. Future directions

We further promote development and validation of these five themes. In particular, themes #1 to #3 are expected to exert clinical efficacy, which will be tested in practical world. In addition to university hospital outpatient/ward, we will examine various models of health care, such as community health care, and home care as joint research. To pursue scientific value of both clinical medicine and medical informatics for the establishment of spatial generalization we will move onto establishing virtual cyberspace for medical/health informatics.

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Introduction and Organization

Clinical Laboratory Center consists of 11 doctors, a chief technologist, 73 technicians, and 3 nurses, 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 2010, 235,386 outpatient blood sampling were performed in this section.

The 2nd Section

This section deals with clinical biochemistry and immuno-serology tests. In 2010, over 4,334,415

serum enzyme tests (such as AST and ALT), and 460,417 immunological tests were performed.

The 3rd Section

This section deals with laboratory hematology and DM-related tests, gene analysis tests and urinalysis. In 2010, 1,000,221 samples were examined for complete blood cell counts, cell surface marker analysis, prothrombin time, fibrinogen, glucose, and HbA1C tests, and 213,693 urine samples were examined.

The 4th Section

This section deals with physiological tests, including circulatory, pulmonary, and neuromuscular function ones. In 2010, 45,796 ECG, 21,324 pulmonary function tests, 19,743 echocardiography tests, 15,643 abdominal echography tests, and 10,051 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 and fifth grade medical students on clinical tests including hematology, chemistry, endocrinology, immunology, bacteriology, cardiology, and pulmonary function. The reversed CPC program is presented to the fifth and sixth grade students. Laboratory practice teaching is provided for the fifth 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) hepatic fibrosis and ischemic reperfusion injury of the liver, 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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Homepage

Introduction and Organization

Operating rooms were centralized for the first time in Japan in the University of Tokyo Hospital on July 1955. Surgical center was located in the surgical ward building till December 1987. The center moved to the new central building on January 1988, when the surgical center had 14 operating rooms, including one bio-clean room. The administration staffs consisted of 4 doctors, 75 nurses, 6 technical officials, 5 part-time employees. The surgical center became to afford services to 18 clinical departments after the new surgical center started.

The total number of operations did not apparently increase between 1999 and 2000, partly because of the limited number of operating rooms and nursing staffs.

In July 2001, the branch hospital, which was located in Mejiro, merged to the University of Tokyo Hospital in Hongo and a new ward building opened in October 2001. Then, the number of elective operations remarkably increased and became over 7500. Efficacy became a key to improve the availability of the operating rooms. Two new operating rooms were tentatively used to overcome the tremendous increase

in the number of elective operations. The one was on the ICU/CCU/HCU floor in the new ward building and the other room was in the outpatient building, which had been used for the orthopedic patients. This operating room was used for the short-stay and day surgery of orthopedics as well.

Until September 2001, the elective operations had been performed daily in 9 operating rooms on average. Then after October 2001, 12 rooms began to be used for elective operations. In the year 2007, the newest central building, which had 11 operating rooms, was open to solve the relative shortage of operating rooms. As a result, the total number of operating rooms became 23, and then the number of operations has been dramatically increased. The number of operations increased thereafter.

A total of 8,485, 9,550, 9921 and 9,944 operations, which counts for 1.5 times comparing to those in 2001, were performed in 2006, 2007, and 2009, respectively. More recently, the number of operations was 10,394 (1,210 emergency cases) in 2010.

There has been much concern about the apparent increase in the patients who undergo laparoscopic/thoracoscopic surgery. There is also an apparent

increase in the number of patients who are positive for the microbiological tests such as tuberculosis, MRSA, *Pseudomonas aeruginosa*, HBV, HCV and HIV.

Activities of Surgical Center

Our works range from the management of operation schedule to the teaching and research.

Management of Surgical Center

All operations of in-patients are performed in 23 operating rooms of the surgical center. Computer system has been introduced in order to deal with the information on the operation. In May 1999, on-line computer system was introduced for ordering system of the elective and emergency operations. Then, the operations have become ordered through the computer terminal of the clinical departments since May 1999. The doctors and nurses became to be able to see postoperative information through the computer system since March 2000.

For the efficacy of the operation, the information on the status of the procedures has been displayed on the computer monitor screen since May 1997. This monitor also tells the hospital staffs whether there are any operating rooms available on the next day. Furthermore, since November 2000, the hospital staffs have become to be able to see how the clinical departments plan the operations through the hospital computer network.

As for digitalized visual information, the photographs of operative fields, resected organs and real-time visual images have been distributed to each clinical department through hospital computer network since February 1997.

In the new ward building, the SPD and progressive patient care system started for the management of our hospital in October 2001. Then, the SPD system was introduced for the surgical center in September 2002.

The complicated surgical procedures including organ transplantation microvascular surgery, cardiovascular surgery, minimally invasive surgery and orthopedic surgery have increased dramatically. In addition, more and more patients recently underwent surgery using artificial implants such as vascular prosthesis, joint prosthesis and intraocular lenses.

The advanced techniques have been employed in the operating rooms. Those include navigation surgery in neurosurgical, orthopedic and ENT (ear, nose and throat) operations, and arterial stent for the thoracic aortic aneurysms. The minimally invasive surgery such as MIDCAB operations is also performed in the CABG as well as in the treatment of heart anomalies such as ASD and VSD. In addition, organ transplantation and intraoperative three-dimensional echo-guided surgery are performed in the surgical center.

Another recent trend is the presence of emergence and re-emergence infectious diseases such as HIV and tuberculosis among the operated patients. Therefore, it is mandatory to educate how to prevent nosocomial and occupational infections in the surgical center. For instance, the principles of standard precautions and transmission-based precautions should be informed to all health care staffs in the surgical center.

The number of immune-compromised hosts and complex surgical procedures will continue to increase throughout the 21 century. Therefore, the surgical center ought to be playing an important role because the improvement of the management skill is mandatory to meet the increase in the perioperative healthcare services for those patients.

Teaching Activities

The following lectures are given to the undergraduates and postgraduates: aseptic techniques, sterilization methods, disinfection methods, prevention of perioperative infections, humoral and cellular responses to trauma and shock, training of scrubbing and gown techniques. Curriculum is updated every year. For example, introductory course for disinfection, sterilization and preservation of surgical instruments and medical devices was added in the training courses in 1998, which gained interest and popularity among 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 so forth. Consequently, education has become one of the most important activities in the surgical center. The lectures

of advanced technologies are in the curriculum for the surgeons, nursing staffs and medical electronics engineers so that they can understand how to use them properly.

Lectures for the nursing staffs consist of a freshman course and an advanced course. The freshman course is a basic training course as a scrub nurse and a circulating nurse. It consists of lectures of aseptic techniques, de-contamination methods, sterilization methods, prevention of perioperative infections, and training of scrubbing and gown techniques as well as aseptic preparation of surgical instruments in the operating room. An advanced course is also prepared to the experienced nurses. The purpose of this course is to upgrade their perioperative nursing skills so that they can afford full nursing skills in the complex surgical procedures such as transplantation surgery, open-heart surgery and neurosurgery.

There is also a training course to medical electronics engineers and students of medical electronics. This training course consists of introduction on the medical electronic instruments and devices, precautions of accidental troubles in handling surgical instruments and medical devices, development of new surgical instruments and 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 staffs and contribute to decrease the number of accidents in handling surgical instruments and medical devices.

The on-job training are given to the non-nursing staffs such as technical officials and temporary employees and performed when they start their careers in the surgical center. They are lectured on aseptic techniques, sterilization methods, disinfection methods, prevention of perioperative infections and how to check the faults in the reusable surgical instruments such as forceps, scissors and clamps. These contents are summarized in the manual. Lectures are also given to senior technical officers and temporary employees to upgrade their technical knowledge and skills.

Research Activities

1) Safety management of the surgical treatments in

the operation center

- 2) Introduction of IT technology in the management of surgical center
- 3) Improvement of cost-effectiveness in the management of surgical center and international comparison of effectiveness in the management of surgical center
- 4) Precautions of accidental troubles in the handling surgical instruments and medical devices
- 5) Introduction of aseptic environment in the operating theaters
- 6) Perioperative infection control of patients undergoing operations and prevention of occupational infection of medical staffs working in the surgical center
- 7) Development of new sterilization methods
- 8) Improvement of cost-effectiveness in sterilization and preservation of medical instruments and introduction of international standardization of sterilization methods
- 8) Cost-effectiveness analysis of disposable and reusable surgical instruments
- 9) Development of new surgical instruments and medical devices
- 10) Improvement of minimally invasive surgery and microsurgery
- 11) Three dimensional processing of visual information
- 12) Computer assisted surgery
- 13) Computer assisted anesthesia
- 14) Inter-hospital visual communications via satellite system

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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, 52 radiological technicians, 2 assistants, 18 nurses, 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 and the nurses of other clinical departments cooperate and are also engaged in the clinical radiology activities. The educational training and registration of the radiation engaging persons are controlled according to the University of Tokyo Hospital Ionizing Radiation Injury Prevention Rules.

Department of Clinical Radiology covers four major fields: (1) Diagnostic Radiology, (2) Radiation Oncology, (3) Nuclear Medicine and (4) the Radiation Safety Control System. The Diagnostic Radiology Section is mainly operated at the first floor in the Central Clinic Building 1. Parts of the diagnostic activities are done at the Central Clinic Building 2 (the MR rooms, the operation rooms, and the emergency department) and some other clinical

departments. The services provided are X-ray imaging, fluoroscopic imaging, computed tomography (CT), magnetic resonance imaging (MRI) and angiography. Radiation Oncology Section is operated at third basement floor of the Central Clinic Building 2. The outpatient clinic is also located here and not in the Outpatient Clinic building. The methods of therapy provided are linear accelerator (LINAC), gamma-knife, Remote After Loading System (RALS) and Brachytherapy (Radioactive Seed Implantation Therapy). Nuclear Medicine Section is operated at the basement floor of the Central Clinic Building 1. The methods of examination provided are conventional scintigram, SPECT and PET. The office of Radiation Safety Control System is located at the third floor of the old Central Clinic Building.

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 fifty MR examinations are done using 1.5-Tesla and 3-Tesla scanners every day. About six angiographies, most of which are interventional procedures including arterial embolization, arterial infusion therapy, arterial infusion port placement, and angioplasty, are done by the radiologists using two angiographic units.

In clinical research works, efficacy of MDCT has been investigated in all parts from the head to extremities. New three-dimensional approaches have been also developed. Clinical research and basic animal experiments are in progress in the field of functional MR imaging and diffusion and perfusion MR techniques.

2) Radiation Oncology:

The radiation therapy is performed with three linear accelerators, an intracavitary irradiation device (RALS), 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. Recently, a new linear accelerator system with cone-beam CT technology was introduced to our hospital, which enabled image-guided radiation therapy.

3) Nuclear medicine:

Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) are the main activities in the clinical and research work. These nuclear imaging procedures are chiefly performed and reported by radiologists and cardiologists. 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] H₂O, CO₂, O₂, CO, [F-18] FDG, [C-11] methionine, [F-18] Dopa, [C-11] NMSP, NMPB and [C-11] raclopride. 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] NH₃, 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. Whole body FDG-PET is one of the most promising studies for exploring metastatic lesions of cancer patients. Combination display of SPECT/PET with XCT/MRI would be a routine job and anatomofunctional images would play an important role in the clinical management of the patients.

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.

Delivery Unit

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Organization

The Delivery Unit of the University of Tokyo Hospital is organized by one professor, one lecturer, 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 864 in 2010.

Recently, cases of obstetrical emergencies like abruptio placentae, eclampsia and uterine ruptures transported from neighboring hospitals have been increasing. Two or 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.]

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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 four 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. Sixteen physical therapists are working in the physical therapy section. In the occupational therapy section, four occupational therapists work for the general rehabilitation service and the other three therapists work for the psychiatric rehabilitation. Four

acupuncture therapists perform acupuncture and moxibustion. In the Day-care Unit, clinical psychologists and nurses also work. In 2006, speech therapists and orthoptists 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 to perform therapy for patients with aphasia, dysarthria, and dysphagia.

Clinical activities

There is not enough doctors arranged for the department of rehabilitation medicine, and we cannot run own beds for rehabilitation patients at present. The professor serves as a director of Rehabilitation Center, the University of Tokyo Hospital. Both departments are united and engage in clinical practice. We have at present no charged ward, and treat about 1,000 new referrals annually from almost all the departments of the university hospital. We always take charge of about 250 patients corresponding about 25% of the whole number of inpatients. We also see 15 people per day at the outpatient rehabilitation setting. The numerical ratio of outpatient is being reduced in order to give priority to the clinical service corresponding to needs expansion of service to inpatients.

Teaching activities

We have provided several clinical curriculums on rehabilitation medicine for 4th, 5th, and 6th year

medical students since 1973. The systematic lecture series for 4th year medical students (M2) include the subjects on rehabilitation for disorders such as cerebrovascular disturbances, spinal cord injuries and spina bifida, neuromuscular diseases, bone and joint diseases, and cerebral palsy as well as on outline of rehabilitation, welfare system, and prostheses / orthoses . We have provided a clinical practice in small group, so-called bedside learning for 5th year students from Wednesday to Friday every other 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 clinical clerkship to our collaborating hospitals with specialized rehabilitation ward.

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

Eleven graduate school students entered by 2006 and six of them acquired a degree of Ph.D. and graduated.

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) Motion analysis of patients with joint disorders in the lower extremities
- 2) Motion analysis of motor development in children
- 3) Early detection, diagnosis, and progression prevention of musculoskeletal disorders in the elderly
- 4) Analysis of motion and energy expenditure in the activities of daily living in the physically disabled
- 5) Rehabilitation approaches for patients with spina

bifida

- 6) Treatment and rehabilitation for patients with congenital limb deficiencies
- 7) Disabilities and handicaps in patients with skeletal dysplasias
- 8) Analysis of musculo-skeletal involvement in congenital insensitivity to pain
- 9) Rehabilitation of patients with hematogenic malignancies around the stem cell transplantation

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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.

The proper staffs in the Division of Diagnostic Pathology include a lecturer, a hospital lecturer, two associates, and three clinical staffs. Dr. Shibahara was promoted to a Lecturer, Department of Pathology on December.

Clinical activities (diagnostic pathology and autopsy)

The annual statistics of the pathologic practice in 2010 fiscal year consisted of 15,502 cases of histological examination (20,515 specimens), 26,370 specimens of cytology, 780 of frozen histology, 639 of intra-operative cytology, 75 of autopsy cases (21% as autopsy rate), and 2 autopsy cases from other hospitals.

Clinico-pathological conferences (CPCs) for the

two autopsy cases are held every month in the hospital. Furthermore, the following surgical pathology conferences are regularly held with each clinical division; the cases of various tumors of organs (the doctor in charge of each), such as thorax (Drs. Ota and Goto), liver, pancreato-biliary tract (Dr. Shibahara), male genitourinary (Dr. Goto) and female genital tracts (Drs. Maeda and Takazawa), breast (Dr. Ikemura), and bone and soft tissues (Dr. Ushiku). Biopsy conferences are also held in the cases of liver (Dr. Shibahara), kidney (Dr. Uozaki) and skin (Dr. Takazawa).

Our aim in the pathologic practices is to provide the correct diagnosis as soon as possible. We are addressing 'one-day pathology' using a newly-developed machine of rapid-histoprocessing. Furthermore, a virtual slide scanner has been installed, which enabled us to save the consultation specimens as digital information.

We are setting out a future providing system of pathologic images for clinical divisions. Dr. Uozaki is mainly in charge of this project.

We have continued to participate the autopsy assessment for "The Model Project for Inspection and Analysis of the Deaths Related to Medical Treatment (DRMT)" of Health, Labor and Welfare Ministry.

Teaching activities

The lectures and exercise course of systemic pathology are for the 2nd grade-students. Bed-side learning (BSL) course of autopsy and surgical pathology are for the 4th grade students. Four students of 3rd grade took the clinical clerkship course.

We instructed all interns to submit one report of CPC case as a requirement of their medical training. The Division of Diagnostic Pathology received four interns in 2010 for the second year program of their internship.

Research activities

Dr. Uozaki carried out a co-operative study with Fuji Xerox and National Institute of Advanced Industrial Science and Technology (AIST) to develop the ontology, expressing diagnoses and macroscopic findings of gastric cancer and the grammar describing

its diagnoses for the pathology report of gastric cancer.

We have finished the two-year project, "Feasibility of Post-Mortem Imaging as a Method Assisting the Autopsy Assessment of DRMT" (Grants-in-Aid from Ministry of Health, Labor and Welfare). The report is now open to public and available at the website of the study group (<http://humanp.umin.jp/>), and the study obtained a high score in the ex post evaluation of the Ministry office. In the study of Tokyo University Hospital, we are now carrying out a research investigating usefulness of post mortem CT images for hospital autopsy, using a CT apparatus in the autopsy assisting CT room. Lecturer Takazawa is in charge of this project.

We continue the pathological studies of neoplastic diseases on the basis of surgical pathology conferences. We are also developing a new antibody-based in vivo imaging and therapy in collaboration with Genome Science Division, Research Center for Advanced Science and Technology, the University of Tokyo. We are evaluating the feasibility of antibody panels for immunohistochemistry to detect the metastasis in the sentinel lymph nodes of the gastric cancer, by constructing the tissue array of primary and metastatic cancers.

References

See the corresponding section of Department of Pathology and Diagnostic Pathology

Department of Corneal Transplantation

Professor

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Introduction and Organization

The department of corneal transplantation was established in 1976 as one of clinical sections in the University of Tokyo Hospital. The purpose of the establishment of this section is to carry out and promote corneal transplantation and to perform clinical and basic research in the corneal diseases and corneal transplantation. The section is composed of a director (associate professor).

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 is held every Wednesday. At the corneal service, we determine indication for corneal transplantation and follow up patients after the surgery. We also diagnose and treat various corneal diseases. The corneal service is conducted by the director and doctors from related hospitals. The patients who enrolled in the corneal service have exceeded 5000. The total number of corneal transplantation has reached 1500 cases since we started keratoplasties in 1971. Approximately 50 corneal transplantations have been performed annually.

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.

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

- 1) Thorough examination of donor eyes not only by slit-lamp biomicroscope but also by specular microscope.
- 2) 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.
- 3) Introduction of sclero-corneal preservation of donor eyes, because sclero-corneal preservation is more suitable for longer preservation than conventional whole eye preservation.
- 4) The long-term natural course of keratoconus has been investigated with corneal topography.

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

1. Regenerative medicine for corneal diseases.

We have pursued to apply regenerative medicine to corneal diseases. In patients with chemical burn of ocular surface and Stevens-Johnson syndrome, we try to reconstruct the ocular surface with autologous cultivated limbal, conjunctival or oral epithelial cells. We also use cultured human corneal endothelial cells, collagen sheet and amniotic membrane to construct sheets with corneal endothelial cells. These sheets have the same degree of pump function as corneal endothelium. We have investigated the potentiality of collagen extracted from animal dermis for reconstruction of corneal stroma. We also examined the potential clinical usefulness of acellularized porcine corneal stroma.

2. Tissue stem cells in the cornea.

Using neurosphere method, we successfully isolated tissue stem cells in the corneal epithelium, stroma and endothelium. Each tissue stem cells show multipotency and self-renewality. We try to utilize these tissue stem cells in corneal regenerative medicine.

3. Meibomian gland dysfunction.

Meibomian glands secrete lipids into the tear film and prevent excessive evaporation of the tear film by forming a thin oily layer on the tear film. Meibomian gland dysfunction (MGD) is a major cause of dry eye syndrome. We have developed a non-contact, less time-consuming, and patient-friendly meibography method that employs an infrared filter and an infrared charge-coupled device (CCD) video camera. Using this meibography system, the structure of the meibomian glands can be easily observed in both the upper and lower eyelids within 1 minute without causing any discomfort to the patients. Using this meibography, we are examining the morphologic changes in meibomian glands associated with aging and sex and assessed their relation with slit-lamp findings of eyelids and tear film function in a normal population.

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Department of Cell Therapy and Transplantation Medicine

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Associate

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Introduction and Organization

Department of Cell Therapy and Transplantation Medicine was institutionally established in 1995, and formally organized in 1996. At present, the staff consists of four medical doctors listed above. 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

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

this strategy is expanding the eligibility of transplant recipients. Allogeneic hematopoietic stem cell transplantations for the elderly are 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, in which the members of Department of Hematology/Oncology and Hematology/Oncology group in the Department of Pediatrics, and some members of Department of Transfusion Medicine routinely participate and discuss on the patients receiving hematopoietic stem cell transplantation.

Teaching activities

Together with the members of Department of Hematology/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 for the second grade medical students. Courses for bedside learning 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. Clinical clerkship courses are given to the fourth 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 tumors, 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. Representative publications from our department published in the past year are listed in the references.

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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 staff of our department is only an associate professor, about 80 doctors from other departments including the department of internal medicine, surgery, gynecology and otorhinolaryngology, participate the endoscopic procedures. The endoscopic rooms moved to the new building in Oct. 2006.

Clinical activities

Endoscopic procedures, including upper gastrointestinal endoscopy, colonoscopy, bronchoscopy, otorhinolaryngological endoscopy and gynecological endoscopy, are performed from Monday to Friday. Emergency endoscopy is performed in the nighttime or holidays. Enteroscopy by using capsule endoscopes and balloon-assisted endoscopes are rapidly increasing in number. Additionally, 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

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
EGD*	6346	7324	7920	7597	8265	8131	8796	9822	10262	10556
Colonoscopy	3212	3529	3873	3728	4084	4327	4360	4679	4996	5152
Bronchoscopy	194	220	207	194	212	201	201	165	226	255
EUS**	479	583	586	476	461	438	484	402	518	551
Enteroscopy	-	-	-	-	-	-	-	133	181	311
Laryngoscopy	154	93	68	61	89	127	91	63	75	70
Colposcopy	181	103	124	139	88	58	117	256	307	361
Total	10566	11852	12778	12195	13199	13282	14043	15520	16566	17256

*Esophagogastroduodenoscopy, **Endoscopic ultrasonography

Research activities

Our researches cover a variety of endoscopic fields in cooperation with other departments.

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Noiri Hanafusa, MD, PhD

Introduction

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.

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].
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.

Medical Care

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.

Research

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. Elucidation of basic mechanisms in cardio-renal syndrome and intervention.
5. Pathophysiology of acute kidney injury and its applicability for renal regenerative study.
6. AKI biomarkers and those clinical significance in ICU/CCU.
7. Renal biomarker to determine clinical actionability in CKD and type-2 DN.
8. The potentiality of urine biomarker tests for developing country [JICA-JST: Science and Technology Research Partnership for Sustainable Development].

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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 division of the hospital and supports not only industry-sponsored, but also investigator-initiated, clinical trials.

With the increasing volume of clinical research conducted in our hospital, demand mounted for the structural framework to support investigator-initiated, especially multicenter, trials.

It is an important mission of university hospitals to develop novel therapeutics by clinical trials. High ethical and scientific standards as well as high reliability are now being required for the implementation of clinical research, including investigator-initiated translational research or trials for the off-label use of approved drugs.

In response to the above demands, the former Clinical Research Center was reorganized in April 2010 into the current Clinical Research Support Center, enabling strengthened support and expeditious promotion of clinical research.

The Center consists 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 for clinical trials and assistance with safety information reporting, and clinical research coordinator activities.

In addition to the existing Consultation Division, the Central Coordinating Unit has added new divisions such as Biostatistics/Data Management Division, Safety Information Division, Operation Division which is responsible for the coordination among the sites, and Monitoring Division responsible for quality control. Activities of these Divisions include protocol formulation, project management, data management, monitoring, statistical analysis and assistance with safety information reporting.

Clinical Research Support Center can now support both trials registered or not registered for marketing approval, and, therefore, can provide seamless support to research in any phase of development.

As of March 2011, the Center staff includes a professor, an associate professor, 3 research associates, 9 pharmacists, 11 nurses, a laboratory technologist

and 4 clerical staff members.

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.

To further improve the quality of trials or clinical research (which includes use of unapproved drugs on a compassionate basis) respecting the principles of the globally standard ICH-GCP, we have prepared and as needed revised the guidelines or SOPs intended for use in our hospital. These documents include those relating to preparation of the study protocol or informed consent form, implementation of research, and handling of costs to trial participants.

For secure process of the applications of industry-sponsored clinical trials to IRB, we hold a preliminary hearing system (named as “protocol presentation”) before IRB.

The items processed by the Center as the IRB secretariat in fiscal 2009 included, as for industry-sponsored trials for marketing approval, 33 new protocol applications, 73 study extension applications, 477 protocol amendment applications, 827 SAE/safety information reports, 36 study closure or termination reports. As for investigator-initiated clinical research, the Center processed 53 new protocols (including 8 applications for compassionate use of unapproved drugs), 149 applications for protocol amendment, 47 SAE/safety information reports, 23 study closure or termination reports.

Protocol presentations of industry-sponsored trials prior to application to IRB totaled 17 applications. Preliminary consultation for investigator-initiated research application including cases of compassionate totaled 108 applications.

To cope with the so-called ‘drug lag problem’ relating to the drugs unapproved in Japan, participation in global trials was an urgent necessity. For this purpose, University Hospital Clinical Trial Alliance (UHCT Alliance) comprised of 6 national university hospitals (Tokyo University, Niigata University, Gunma University, Tsukuba University, Tokyo Medical and Dental University and Chiba University) located in the central part of Japan was

established in 2006 and has since been in collaboration toward improvement of clinical trial environments. In 2006, the rotated managerial site was Tokyo University, where the Alliance Office was based. In Alliance an organizational structure has been established that can cooperatively attract trials and smoothly process them for IRB approval. A scheme to educate the staff in preparation for global trials has been put in place. In 2007 Shinshu University joined the Alliance as the 7th member university.

From April 2009 on, a 5-year special research grant from the Ministry of Education, Culture, Sports, Science and Technology for the promotion of UHCT Alliance allowed to set up a full-time office (made up of 2 staffers) and further expand the activities. Operational subsidies that Tokyo University received were distributed to each university based on a joint project agreement, which was an unprecedented attempt for our university. Each university and the Office was given its own task to cooperatively promote the mission of the whole Alliance.

Until the end of March 2011, 49 protocols were introduced to the Alliance including 25 multinational trials. The Alliance helped to assess feasibility in 8 trials and to select the participating sites in 33. Cooperative protocol presentation (hearing) sessions were held for 36 protocols. Industry sponsors applied for regulatory drug approval from Ministry of Health, Labour and Welfare based on data of 11 trials and 4 drugs have been so far approved.

Clinical Research Support Center managed drug/device inventory for 86 clinical trials for regulatory approval, 2 postmarketing trials, 4 trials of devices, 47 investigator-initiated clinical trials, one case of compassionate use in fiscal 2010. The number of prescriptions processed was 797 for trials for approval and postmarketing trials combined, 652 for investigator-initiated clinical trials. We are currently managing trial drugs centrally for 2 multicenter double-blind trials. We are also in charge of the primary review of clinical trial safety information and of maintaining the database on clinical trials in general.

Clinical research coordinators (CRC) of the Center have been supporting as a principle all clinical trials for approval and postmarketing trials since 2002. We started partially supporting investigator-initiated trials

in 2004 and have already supported 5 trials. In 2005 we started providing CRC support to investigator-initiated trials on a beneficiary-pays basis and have already supported 6 trials. CRCs exclusively involved in investigator-initiated trials have been employed as needed. The number of trial participants that CRCs interacted with was 3777 in fiscal 2006, 4853 in 2007, 5172 in 2008, 4761 in 2009 and 3776 in 2010. We started receiving monitoring visits for every trial participant's data in 2002. The number of monitoring visits increased to 569 in 2007, 952 in 2008, 840 in 2009 and 672 in 2010.

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

Our outpatient clinic for trial participants was moved to the second central clinic building, which was newly opened in November 2006. The new clinic has reception desks for consultation and own waiting space.

At Central Coordinating Unit, which was newly established, 5 projects were adopted for full support by the Center including project management, data management etc.

Teaching Activities

Two resident physicians got training for a month in the Center as part of the M.D. residency training program. Ten students in the Graduate School of Medicine also got one-day training. Three trainees from outside the University got CRC training for 3 weeks. One trainee got similar CRC training for a week.

Annual CRC training course for national, public and private university hospitals in 2010 was held under the auspices of Tokyo University Hospital for 5 days, in which 82 trainees from university hospitals all across the country participated.

Dr Arakawa also gave lectures in a lecture series on clinical science for graduate course students of the Faculty of Pharmaceutical Sciences

An international symposium for clinical research was held on March 11, 2011 as a 10th memorial seminar. Although we met a big earthquake, the

symposium itself could be continued to the last speaker with the change of venue.

Research Activities

An endowed course on clinical trial data management was opened in April 2007 with the cooperation from the Center and the Biostatistics Department, Graduate School of Medicine, conducting research and education on data management and biostatistics focused on practical application to trials.

The Center was involved in 4 scientific meeting presentations, 20 invited lectures in fiscal 2010 and 12 published papers in 2010. There was one news media article that reported on the Center.

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University hospital Medical Information Network (UMIN) Center

Professor

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Instructor

Hirono Ishikawa, Ph.D.

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

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. On October 1, 2004, Ms. Hisako Matsuba arrived to take on the position of research associate that is a lower part diverted the associate professor position. She resigned from her position at the end of March, 2006, and Dr. Noriaki Aoki, formerly an assistant professor at the School of Health Information Sciences, University of Texas Health Science Center at Houston, became associate professor at the Center. 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 290,000 registrants, and approximately 40,000,000 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' Education:
<http://www.umin.ac.jp/education/>

A Web-QME:

Web-based Quality Management System for Education

SUPERCOURSE:

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

VHP: Visible Human Project Image Data

EPOC: Evaluation System of Postgraduate Clinical Training

Debut: Dental Training Evaluation and Tabulation System

■ Medical Examination and Treatment

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

- Intoxication database
- HIV treatment manual
- Medical supplies and materials database
- Drug information text database for patients
- Drug information text database for pharmacists
- Standardized nursing procedures database
- Ministry of Education, Culture, Sports, Science and Technology document public information system
- Basic hospital statistics database
- National university hospital-related medical dispute report
- Collection of advanced medical procedures application
- 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
- Video-on-demand (VOD) and streaming service

(3) Communication support

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

Teaching Activities

We provide briefing sessions and symposiums to disseminate and promote services offered by the UMIN center. In 2005, the UMIN Center held briefing sessions and symposiums for medical supplies adverse event report system, thalidomide registration system, clinical test registration system, and dental training evaluation system. In 2006, we held briefing sessions and symposiums for Safety Management System for Unapproved Drugs, Individual Case Safety Reports. These sessions and symposiums were broadcasted through the MINCS system, and can be downloaded as VOD from the UMIN server. Please refer Department of Health Communication for detail information about graduate and undergraduate education.

Research Activities

Please refer to the Department of Health Communication about research activities.

References

See Department of Health Communication page

Organ Transplantation Service

Director and Professor

Norihiro KOKUDO

Homepage <http://www.h.u-tokyo.ac.jp/patient/depts/1512ishokugeka/index.html>

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 400 cases of living donor liver transplantation has been performed, and the 5-year survival rate is around 85% which is much superior to the national average (~70%). The University of Tokyo Hospital has been one of the authorized institutions for heart transplantation and deceased donor liver transplantation.

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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 eight physicians

(four regular physicians and four 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 two 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) 2010 from April 1, to March 31, 2011, the total number of examinees (who had basic examinations and optional examinations) was 5,851, including 1,987 in basic examinations, 434 in complete cardiovascular examinations, 24 in home blood pressure screening, 459 in complete cerebrovascular examinations, 67 in check up dementia, 331 in colorectal cancer screening, 367 in uterine cancer screening, 428 in breast cancer screening, 552 in lung cancer screening, 653 in tumor marker diagnosis, 466 in estimation of gastric cancer risk, and 75 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 2010, we issued 881 letters of referral to other departments in our hospital and 98 to other hospitals.

We have expanded our public relations efforts and during the FY 2010 our brochure has reached its second edition and 25,000 copies were delivered. We also prepared posters which were placed within our hospital and on the campus of the University of Tokyo as well (60 posters). Our homepage (the above URL) has been constantly updated to provide the latest information for examinees.

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in patients with bicuspid aortic valve: insights from the International Registry of Acute Aortic Dissection (IRAD). The American College of Cardiology 59th Annual Scientific Session (March 14-16, 2010, Atlanta, GA, USA)

Division of Tissue Engineering

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Introduction and Organization

Division of Tissue Engineering was established as a special medical office in The University of Tokyo Hospital, in October 2001 and has a fully equipped 800 m² laboratory on the 8th floor of the Inpatient Ward B. Division of Tissue Engineering consists of Department of Bone & Cartilage Regenerative Medicine, Department of Vascular Regeneration, Department of Clinical Renal Regeneration, 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 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 Inpatients Ward B.

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

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

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

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

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

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

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

Research activities

As for corneal regeneration, we aim at construction of regenerated cornea, clinical application of corneal epithelial sheet transplantation for ocular surface reconstruction and establishment and clinical application of corneal endothelium transplantation. To achieve these goals, we are conducting functional analysis on cultured corneal cells, reconstruction of

cornea with cultured epithelium and endothelium, and artificial stroma, research on adult stem cell biology in corneal tissues and immunological analysis on amniotic membrane for ocular surface reconstruction

As for vascular regeneration, we aim at establishment of effective and safe “therapeutic angiogenesis” and its clinical application, development of non-invasive soft-tissue reconstruction technique assisted by induction of angiogenic reactions and development of the techniques to induce microcirculation to regenerated organs. To achieve these goals, we are conducting research on angiogenic gene therapy using adenovirus vector, research on angiogenic gene therapy using non-viral vector, development of drug delivery method for therapeutic angiogenesis and research on induction of angiogenic reactions in soft-tissue.

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 nanomicelle 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.

As for renal regeneration, we aim at clinical application of kidney-derived adult stem cell, clinical application of new scaffold material and matrix for renal regeneration and clinical renal regeneration by using cord blood. To achieve these goals, we are conducting research on adult stem cell biology in regeneration, comprehensive research on stem cell dysfunction in renal failure and development of 3-D culture system for induction of metanephros in vitro.

As for regenerative medicine for hematopoiesis, we aim to develop effective systems for in vitro expansion of cord blood hematopoietic stem cells (CB-HSCs) and its clinical application to human hematopoietic stem cell transplantation, and for

inducing various hematopoietic components from HSCs and embryonic stem cells. To achieve these goals, we are conducting research on the regulatory mechanisms of proliferation, self-renewal, and differentiation of human hematopoietic stem cells (HSCs), plasticity of HSCs and clinical application of the in vitro expansion and differentiation system of HSCs.

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. On Mar 18th 2011, our clinical study "Development of implant-type tissue-engineered cartilage for patients with nasal deformity in cleft lip and palate" was authorized to conduct after being discussed based on "Guideline for Human Stem Cell Therapy Clinical Research".

In the laboratory for pediatric regenerative medicine, we are doing research to fabricate an engineered airway by cells originated from trachea tissue. In addition, the fundamental study of the amniotic fluid cell is performed to create new therapy for new born babies.

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 and Department of Bone and Cartilage Regenerative Medicine are 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 in the

four departments as a result of basic research. In Project for Regenerative Medicine of Hematopoiesis, clinical study on expansion of human cord blood hematopoietic cells (Institutional Review Board approval number #351) has been started. In Department of Vascular Regeneration, clinical studies on claudication limbs and severe ischemic limbs caused by peripheral vascular diseases (IRB approval number #825 and #826) have been started and continued without causing major side effects. In Department of Corneal Tissue Regeneration, clinical studies on transplantation of cultured autologous oral mucous epithelial sheet on amniotic membrane for ocular surface reconstruction, and corneal endothelial stem cell transplantation for decrease in number of corneal endotheliums (IRB approval number #363 and #898) have been started. 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, the clinical study "Development of implant-type tissue-engineered cartilage for patients with nasal deformity in cleft lip and palate" was authorized to conduct on Mar 18th 2011, and is supposed to start soon. As stated above, we are proceeding translational research aiming at clinical application of tissue engineering and regenerative medicine.

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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Hospital Planning and Management

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Introduction and Organization

In recent years, the medical system in Japan has been experiencing times of major change. University hospitals, as well, have been under pressure for sweeping reforms. There are demands, greater than ever before, for the development and practical application of high-quality advanced medical treatment, and for the efficient promotion of graduate and postgraduate education, and of clinical research. And there are demands for those results to be expressed clearly to Japanese citizens in specific terms. In April 2004, as the University of Tokyo was incorporated under the National University Corporation Law, the University of Tokyo Hospital underwent drastic organizational restructuring. In addition to the establishment of Hospital Executives, there was also the launch of four organizations that support hospital management (Hospital Planning and Management; Personnel Administration and Human Resources; Performance Monitoring, Risk Management, and Staff Development; and Education and Research Support) and three organizations that support clinical management (Inpatient Service Administration; Outpatient Service Administration; and Central Hospital Service Administration).

Hospital Planning and Management is a key working organization in the management of the hospital. It has two full-time faculty members from the Department of Planning, Information and Management, and boasts a team of two pharmacists,

two nurses, one engineering staff member, and 12 administrative staff.

Clinical activities

Hospital Planning and Management is responsible for all of the organizational and strategic business affairs of the University of Tokyo Hospital. It conducts the following kinds of clinical-management duties.

(1) Analysis of hospital management

The division manages and analyzes hospital accounting information, and conducts hospital management analyses by utilizing management information and standardized hospital information.

(2) Planning

Based on the hospital management analyses, the division designs short-term management planning and strategy, and provides effective support for the Hospital Executives to make swift management decisions. The division is also responsible for formulating medium- and long-term plans. Following is a list of hospital management achievements in which Hospital Planning and Management was deeply involved.

- “22nd Century Medical Center” launched
- new central hospital building launched
- Enhanced functions in the inpatient ward (expansion of ICU/CCU, increase in number of beds in the Psychiatry Department, GCU and

MFICU, expansion of GCU)

- To reduce the average length of hospital stays, and improve the bed occupancy rate
- To achieve reduce drug costs and costs for medical materials
- Critical Care Center launched

In addition to these achievements, the division has also strived to improve innovative patient services, such as introducing a credit card for patients, attracting commercial stores in the hospital, and illuminating the hospital buildings. At the same time, the division has worked to develop an environment in which medical care staff can provide high-quality and safe medical treatment in a more composed fashion.

(3) Medical policy recommendations

The division is not just restricted to the management of the University of Tokyo Hospital. It also actively implements policy recommendations aimed at improving the medical system in Japan and at deregulating medical care.

Furthermore, we point out issues related to Japan's medical insurance system based on evidence, and we constantly issue messages for their improvement.

Teaching activities

Turning to postgraduate education, the division accepts 1 doctoral student from the Department of Medical Informatics and Economics at the Graduate School of Medicine, and 1 research student from the Graduate School of Medicine.

Postgraduate students and research students pursue their own research projects, not just from the research areas of healthcare management and hospital management, but also from such areas as healthcare economics and healthcare policy. The students review previous literature and materials, and they are actively engaged in developing research designs and the collection of data. The students present regular research progress reports, they are given thorough instruction on writing academic papers, and they also follow a rigid schedule of academic presentations.

Research activities

The research activities of the division are not limited to merely healthcare management and hospital management, but cover a broader area, including health policy and health economics.

(1) Research in healthcare management

In the past, the division analyzed the impact that a prospective payment system, which is based on Diagnosis Procedure Combination (DPC), has on the healthcare workplace, and it conducted research to estimate the effects that this system has on the length of hospital stays. The division also conducted research related to the efficient use of medical facilities, by studying the relationship between the running of operating rooms and the number of hospital beds.

In an attempt to systemize healthcare management, the division edited a standard textbook.

(2) Research in healthcare policy

The division undertook comparative studies between medical systems in Japan and other developed countries. Empirical studies related to the disparity in domestic and imported prices of medical materials among multi countries, and studies into the career paths of medical doctors and health workers' migration are ongoing.

The division carried out assessments related to Japan's medical insurance system, and in particular, conducted research into improvements to the prospective payment system based on DPC, and the effectiveness of such improvements.

(3) Research in healthcare economics

In cooperation with hospitals providing cares for HIV/AIDS patients, the division is conducting cost-accounting study in HIV/AIDS care. Recently, we began cost-effectiveness analysis for hepatitis B prevention strategies.

(4) Other research topic

The division commits a research project regarding socio-economic impacts on childhood obesity using a large panel data set, with other research institutes

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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 multidisciplinary approach by working in collaboration not only with the Department of Neuropsychiatry, Department of Pediatrics and Graduate School of Education in the University of Tokyo but also several other educational and/or clinical facilities on mental development or developmental disorders. The Department of Child Psychiatry complemented the Clinical Education Center by providing fieldwork for clinical training and offered clinical services to patients with various development problems also.

The Clinical Education Center of Mental Development was closed in March 2010 because of time limit of the fund, and Department of Child Neuropsychiatry, Graduate School of Medicine was established in April 2010. The Department of Child Psychiatry, as the clinical counterpart to the department in graduate school, focuses on clinical

activity related to research as well as quality practice of child psychiatry and education of leading child psychiatrists and allied professionals. In addition to 3 professors of the graduate school, 2 psychiatrists and 3 psychologists are officially assigned to the Department of Child Psychiatry.

Clinical activities

In the year 2010, the Department of Child Psychiatry consisted of 8 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).

With reconstruction of clinical activity, the number of new patients was limited to less than 200 in the year 2010. A large part of the new patients consisted of patients with ASD, tic disorder or ADHD. Although establishment of Tic/OCD clinic might make a slight change, general trend of the patients were similar to that of the previous year.

The follow-up clinic consisted of general clinic and special clinics (high-functioning ASD clinic and 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 clinics meet a need for high level services and work with research for special diseases.

Clinical activities are largely divided into two areas of general child psychiatry outpatient services and interventions for individuals with developmental disabilities.

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.

Interventions for developmentally disabled individuals consist of “developmental psychology outpatient services” and “short-term group therapy”. Patients involved in interventions are individuals with developmental disabilities, and individualized treatment based on cognitive developmental therapy is planned for each. “Developmental psychology outpatient clinic” provides 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). One of “short-term group therapy” is a 10 session group therapy for a small group of preschool children with ASD. Another is a 10 session group therapy for adults with high-functioning ASD, and started in 2010. These services are provided mainly by psychologists under the supervision of child psychiatrists.

In addition to these outpatient services, trial of “inpatient assessment on developmental disorders” service started in 2010. This service 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 “short-term group therapy” for preschool children. Graduate students in clinical psychology course from several universities participate in “short-term group therapy” for preschoolers also.

One month training course is offered to junior residents in pediatric specialty course and senior residents of neuropsychiatry. This course includes intake interview of first visit patients, observation of assessment and treatment for follow-up patients and “short-term group therapy” for preschoolers, and visit to community hospital and intervention/guidance facilities for child and adolescent mental health.

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

The reexamination of reliability and validity of Ohta Staging (an evaluation system using symbol development for cognitive developmental therapy developed in the former child division of the Department of Neuropsychiatry) and investigation of the effectiveness of present interventions for children with ASD are being conducted.

A comparison study of the effectiveness of individual treatment and “short-term group therapy” in a randomized control study is being undertaken.

In another study, 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.

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

Research exploring susceptibility genes of ASD in chromosome 2, long arm of chromosome 7 and long arm of chromosome 15 are conducted. As we are interested in gene-environment interaction, we are examining influence of age of parents and assisted reproduction technologies on emergence of ASD. Investigation of specific family and environment of Tourette syndrome is being undertaken also.

Neuroimaging

Studies include structural MRI, MEG, 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, ADHD and Tourette syndrome 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 by delayed reward task is in process.

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Department of Palliative Medicine

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

History and outline of organization

Half of the cancer patients die of original cancer in spite of the advanced cancer treatment technology. The success or failure of the first treatment against cancer results in its cure or non-cure. Almost all the patients who underwent unsuccessful initial treatment die after the struggle against disease within several years. It is sure to need the proper medical care only for such patients.

However, most attention has been entirely paid to the improvement of cure rates of cancer patients in Japan so far. Therefore, the sense of palliative care is very poor and immature consequentially.

Palliative care means active treatment approach and a total human care for the patients who do not respond to any treatment. In addition, pain relief, other symptomatic controls, psychiatric, social and mental care are as a top priority for these patients. However, palliative care is necessary to be applied in the cancer treatment even for patient in early stage of the disease as well as the progressive disease.

In Department of Palliative Medicine of The University of Tokyo Hospital, our palliative care team takes a leading role not only to control physical symptoms of patients but also to care for the mind and social support at the same time, and to improve the overall QOL (Quality of life) of patients. Moreover, it also becomes base of the education and palliative medicine research for medical students.

Palliative care is described clearly in "Fundamental law of the cancer measures" passed in the National Diet on June 2006, "The medical treatment to aim at relieving pains according to the condition of cancer patient is appropriate from the early stage of the disease". In a word, palliative care is provided by the law as a medical treatment that should be offered at

the early stage when the patient receives the cancer treatment.

Consultation

In The University of Tokyo Hospital, the palliative care team is composed of a lot of specialists such as one full-time staff doctor, one full-time doctor, and the designated hospice care nurse who take an initiative in working. They visited the general ward and offer palliative care to the patient who has received the cancer care in cooperation with patients' attending doctors and ward staff and rehabilitation staff, etc.

Hereafter, we concretely show the consultation situation in fiscal year 2010.

The cumulative number of patients who consulted our palliative care team was over 2000 (20.3 average daily patients). The maximum monthly patients were 47 of January (28.9 daily patients). According to site of the cancer, 415 cancers were divided into 62 lungs, 42 stomach, 38 pancreas, 28 ovaries, 27 uterine, 21 esophagus, 19 breasts and so on. We visited almost all the ward in the hospital. These figures proved significantly the importance of the palliative care.

Education

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

1) Palliative care training program

The training course (selection) for two months (or * for one month)

- Program to acquire basic knowledge and technology of palliative care for targeting all resident physicians. * Only in "Comprehensive Internal Medicine" selection.

The training course (selection) for four or eight months

- Program to acquire basic knowledge, basic technology, and communications skills for doctor who aims at medical oncologists or palliative care doctor.

2) Curriculum

Resident physician arrangement and content of training

- All resident physicians are assigned to the palliative care team. They chiefly participate in ward palliative care as a member of the team, and also learn the cancer registry of palliative care.
- In the course for four and eight months, they make palliative care program for patients in charge, discuss their palliative care with patients' attending doctors, ward staff, and execute their palliative care program.

Content of training and attainment goal

- The ward palliative care (3-5 patients in charge per month and around 25 consultation patients a day): They acquire the outline of control of physical and psychiatric symptoms of the patients with common disease in Japan such as digestive cancers in the general ward. They also acquire the outline of spiritual and family care.
- Cancer registry: In The University of Tokyo Hospital, it is not unusual that the patient whom the 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 concise and plain content of the offered palliative care for such a patient to the data base. They acquire the outline of data management of the palliative care connected directly to a clinical research.
- The communications skills: The clinician should tell "Bad news" time after time by all the processes of examining the patient. It is very difficult for the

clinician to explain the accurate information of diagnosis, progression and prognosis of cancer to the patient. This is a lot of work of the stress to the clinician. The clinician should deal with patient's disappointment or failure feeling when treatment does not go well while should do the balance of "Bad news" and "The patient's hope and expectation". We introduce Protocol (SPIKES) of the communications skills that psychiatrically support the patient in Department of Palliative Medicine of The University of Tokyo Hospital. Resident can make the palliative care execution program based on this Protocol, and intend to obtain the communications skills in the course of four or eight months.

Event concerning education

- Concerning the intensive course to the first stage resident physicians, following lectures are done by the staff.
 - O pain control
 - O delirium control
 - O Introduction of the guideline and its use
 - O Basic drug therapy for palliative care
 - O Spiritual care for Japanese

Clinical training schedule

- Conference: Monday - Friday (every day) 9:00-10:30
- Ward consultation: Monday - Friday (every day); up to the end of request patient's consultation after conference.
- The cancer registry: They input data in the ward round with the HIS (Hospital information system) terminal on each floor.

System of guidance

- The ward consultation: Resident participate in the consultation team (or palliative care team) that consists of two guidance medical doctors (one assistant or lecturer, one designated hospice care nurse, and one resident physician). A palliative care team examines about 20 – 30 in-patients a day.
- The conference: Psychiatrist, morphine special pharmacist, and nurse of The Tokyo University Graduate School of Medicine and others participate in the daily conference besides the regular member of the palliative care team in the ward round. They discuss the multidisciplinary palliative care program that the palliative care team offers. They

also guide the resident's palliative care program from their special viewpoints.

Research

The content accumulated from the palliative care consultation is input to the data base concise and plainly, and submitted to the international medical journal such as "International Journal of Radiation Oncology Biology Physics", "American Journal of Hospice & Palliative Medicine" and "Biomed" as a result of a clinical research.

The following fields of investigations are the one that had been executed in our Department of Palliative Medicine. Please refer to the homepage for results in details and acquisition of the research fund.

- 1) Evaluation and quality assurance of special palliative care team
- 2) Development of the scale to measure execution of preferable death and its nationwide investigation
- 3) Development of target system in extracranial stereotactic radiotherapy
- 4) Home care of cancer patients in terminal stage and regional liaison
- 5) Palliative care supporting metastatic breast cancer patient
- 6) Chinese medicine in palliative care

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Clinical Genomics

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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), dermatologists, 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 Wednesday 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 we started pharmacogenetics tests in 2006. Those include tests for proton inhibitor, warfarin, irinotecan, and tacrolimus.

We provided the lectures entitled as "Seminar for Clinical Genetic Medicine".

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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, Clinical Vascular Regeneration, Bone & Cartilage Regenerative Medicine, Cartilage of Bone Regeneration, Department of Immunotherapeutics (Medinet)

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

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

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

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

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

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

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

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

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

Research activities

Development of Advanced Stereotactic Radiation Cancer Therapy System

Department of Radiation Oncology

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

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.

Laboratory of Medical Ultrasound with Microbubbles in Oncology

Department of Mechanical Engineering, Fluids Engineering Laboratory

Department of Surgical Oncology

To develop easy, precise, non-invasive systems to treat human disease. To devise a method to induce microbubbles effectively to treat human tumors in deep situ. To make a precise assessment on tumor invasion in μm order by injecting microbubbles into tumor arteries. To develop a non-invasive treatment system using HIFU device and microbubble contrast agents.

Medico-engineering Laboratory for Microsurgical Robotics and Virtual Simulation Laboratory (MRV Labo)

Laboratories of A Morita, Neurosurgery

Dept. Engineering Synthesis, M Mitsubishi

To develop Microsurgical robotic system and 3D visual system for telesurgery

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

Department of Pharmacoepidemiology

Chemical System Engineering

Department of Clinical Epidemiology & Systems

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.

Surgical Robot System Lab.

Robotics, Dynamics, and Control Laboratory

Department of Mechano-Informatics

University of Tokyo

Development of motion synchronization technology for in-vivo molecular imaging of small animals, based on robot systems for endoscopic cardiac surgery. Neuro-musculo-skeletal model and its parameter identification for diagnosis and rehabilitation of neuromuscular disorders.

Vascular Biomebical Engineering Laboratory

Department of Vascular Surgery

Department of Tissue Engineering, The University of Tokyo Hospital

Bio-Medical Precision Engineering Laboratory, Department of Precision Engineering, The University of Tokyo

Development of minimally invasive diagnostic and therapeutic technologies for vascular surgery through collaboration research.

Orthopedic clinical biomechanics laboratory

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.

To develop a new method for evaluation of fracture healing by echo tracking.

To develop a non-invasive method for morphological evaluation of articular cartilage.

To develop a device for assisting in fracture reduction and fixation.

Minimally invasive cardiac surgery with the integral videography system

Department of Cardiothoracic Surgery, Graduate School of Medicine, University of Tokyo

Advanced Therapeutic and Rehabilitation Engineering Laboratory, Department of Mechano-Informatics, Graduate School of Information Science and Technology, University of Tokyo

To develop: real-time three-dimensional echocardiography, suture device with liner probe, integral videography, and minimal invasive cardiac surgery monitored by real-time three-dimensional echocardiography without cardiopulmonary bypass

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 develop more effective immunotherapeutic approaches.

Molecular Imaging Laboratory, Cooperative Unit of Medicine, Engineering and Pharmaceutical Research

Tetsuo Nagano, Laboratory of Chemistry and Biology, Graduate School of Pharmaceutical Sciences

Yasunobu Hirata, 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 a novel device for bioartificial pancreas and 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

Islet transplantation has potential to become the most physiologically advantageous and minimally invasive procedure for the treatment of type 1 diabetes mellitus. The most serious problem is that long term insulin independence of five years has been substantially still quite low. Our concern is to improve poor long term insulin independence, of which the one cause is considered to be transplant site.

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.

Laboratory of 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 signal transduction pathways of major adipokines including adiponectin

Laboratory of Biomaterial Science

Department of Orthopaedic Surgery, Faculty 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

Molecular and cellular mechanics laboratory for the development of multi-scale heart simulator

Department of Cardiothoracic Surgery, The University of Tokyo Hospital

Biomechanics Laboratory, Graduate School of Frontier Sciences, The University of Tokyo

We are developing multi-scale, multi-physics heart simulator for the in-silico diagnosis and treatment of heart diseases by the synergistic effort of cellular physiology and computational mechanics. For collecting quantitative data for the simulator, mechanical analysis of cardiomyocytes is performed.

Laboratory of Hard-Tissue Nanomedicine

Kataoka & Yamasaki Lab, Department of Materials Science, Graduate School of Engineering, The University of Tokyo

Department of "Menicon" Cartilage & Bone Regeneration, Graduate School of Medicine, 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 gene delivery system by supramolecular nanotechnology. 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

Cooperative Unit of Kataoka Laboratory and Department of Vascular Regeneration

Department of Vascular Regeneration, Division of Tissue Engineering, The University of Tokyo Hospital
Kataoka Laboratory, Department of Materials Science and Engineering, Graduate School of Engineering, The University of Tokyo

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

facilitated internalization by the targeted cells through specific interaction of the pilot molecules. Currently, our research has been focused on in vivo gene transfer to artery walls and muscles using polymeric micelles incorporated genes.

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Medical Specialists Training Center

Associate Professor

Nobuyuki Shimizu, M.D., Ph.D.

Homepage

Introduction and Organization

The Region-based Advanced Medical Specialists Training Promotion Center was established in April 2009 under the Personnel Affairs Department with the aim of addressing the shortage of doctors and the decreased number of doctors on loan from university hospitals, which are serious social issues nowadays. Efforts are focused on establishing a circulating career development system for medical professionals in close cooperation between the University of Tokyo Hospital and regional medical institutions.

Outlines

- 1) Serving as the contact point of the University of Tokyo Hospital (the University Hospital) for other hospitals with which the University Hospital has personnel exchange programs (hereinafter as the “partner hospitals”), the Center regularly gathers information on these partner hospitals and discusses their needs in order to promote interactive personnel exchanges.
- 2) The Center communicates gathered information regarding vacant positions of partner hospitals and qualifications to relevant clinical departments/divisions of the University Hospital so as to help fill the positions with doctors of the University Hospital.
- 3) The Center also helps doctors of a partner hospital to receive training at the University Hospital for a certain period of time, on request basis from the partner hospital, in order to improve their medical skills and experience.

Characteristics

The Center offers assistance not only to physicians

and dentists but also to nurses, pharmacists and other medical professionals in their career formation. Efforts are focused on improving training systems and environments at partner hospitals and establishing a network between the University Hospital and its partner hospitals. Thereby, it is aimed to further improve the education and training capabilities and clinical research capabilities of the University Hospital.

The Center will propose a model curriculum for a career development system for medical professionals based on interdisciplinary, interactive exchange among medical staff from different clinical departments/divisions and laboratories of the University Hospital and its partner hospitals.

University Hospital

Pharmaceutical Service

Department of Pharmacy

Professor

Hiroshi Suzuki, Ph.D.

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Introduction and Organization

We have 9 faculty members, 62 pharmacy staffs, 8 pharmacy residents, and 15 graduate students and 5 undergraduate students from the faculty of pharmaceutical sciences and 4 graduate students from the faculty of medicine (as of December 1st, 2010). In addition, project associate professor (Akihiro Hisaka, Ph.D.) and project research associate (Yoshihide Yamanashi, Ph.D.) from Pharmacology and Pharmacokinetics department, and project research associate (Shogo Miura, Ph.D.) from Cancer Professional Training Plan are 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 the medical person, 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 contraindications 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 bar code 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 the patient 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 safekeeping of all the in-hospital medicines (approx. 2,300 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 pharmacy department), 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 1st and 2nd ICU section.
- ② Arrangement and mixing of injections for patients at the staff station of Hematology and Oncology.
- ③ Investigation of carrying medicines and the side effect histories, allergy histories etc. at the time of hospitalization. Participation for conferences. Procurement and appraisal of patient's basic information about the disease, compilation of the medicine history. Monitoring of medication guidance and the side effect for the patient, 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 2010)

Number of items on in-hospital formulary: 2,303

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

out-patients	:	468,245 ps.
(outside	:	379,647 ps.)
(inside	:	88,598 ps.)
out-patient chemotherapy:		7,522 ps.
in-patients	:	214,467 ps.
injection drugs	:	225,155 ps.
IVH	:	8,834 pp.
chemotherapy	:	10,870 pp.

TDM consultations (annual) : 16,585

Numbers of hospital pharmaceutical cares (annual): 5,361

Educational Activities

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 health sciences and nursing. We also have our own one-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 free quarter practice course for some M1 and M2 students for 2 weeks and teach basic molecular and biochemical techniques as well as the pharmacokinetic theory to them. We are providing a 3-days practice course as a part of compulsory clinical practice for the M3 and M4 students and teach clinical pharmaceuticals and practical knowledge of prescription and risk management to them. For the students in the health sciences and nursing, we are in charge of clinical pharmacokinetics lectures as a part of a compulsory subject, "Pharmacology and Toxicology".

For students in the faculty of pharmacy, we are in charge of two series of lectures for the undergraduate students: "Clinical Pharmacy I" (compulsory subject) and "Clinical Pharmacy II" (an optional course). 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 these, 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 the pharmacists at the hospital is one of the most important curriculums. In 2010, we accepted total 42 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. On the other hand, 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 2010, 8 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 activities

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 effect. We need to understand not only the detailed molecular machinery of drug target, but also its environment surrounding the target (ex. other associating 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 / the 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 side-effect of drugs directed against particular molecular target. Finally, these outputs would be feed backed to early drug development stages.
4. Elucidation of the molecular mechanism related to the side effect of drugs using large-scale “-omics” analysis. Finally, the quantitative information would be applied to develop strategies to prevent / treat the side 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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**Center for Disease Biology and
Integrative Medicine**

Laboratory of Molecular Biomedicine for Pathogenesis

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Research

Our laboratory will focus 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 will give high priorities to *in vivo* analyses. This will definitely contribute to the direct therapeutic application of our findings. Since our rationale is to challenge to uncharacterized disease mechanisms and physiologies, we will not restrict our interest, strategy or technique employed, in certain specific field. Rather, we will expand our research area by establishing different collaborations with a broad spectrum of investigators. 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. The major specific aims during the next five years are as follows:

1. Role of Apoptosis Inhibitor expressed by Macrophages (AIM) in atherosclerosis development.

AIM, which we initially identified as a soluble apoptosis inhibitory factor, is largely produced by tissue macrophages. Recently, we found that AIM expression induction is highly correlated to hyperlipidemia; and that expression of AIM is critical in progression of atherosclerosis as assessed in AIM knockout mice. We will isolate the putative receptor for AIM, and elucidate the entire signaling pathway of how AIM inhibits apoptosis. In addition, by generating functional antibodies against human AIM, we will develop a potential treatment of atherosclerosis by suppressing AIM activity in the body.

2. Epigenetical regulation of Genome-Stability via Polycomb and its relevance to oncogenesis.

Recently, we discovered a novel Polycomb group protein MBT-1, which specifically dictates the maturational transition of immature myeloid progenitor cells. We will clarify the definitive molecular mechanism of how MBT-1 regulates the myelopoiesis, which may open avenues for the further understanding of the mechanisms responsible for leukemogenesis. In addition, we will perform a large scale screening of leukemia patients for the mutation

and/or the translocation of the MBT-1 gene (locus).

3. Regulation of mitosis progression by DEDD and its influence on cell & body sizing and oncogenesis.

It has been suggested that the regulation of apoptosis is crucially involved in tumor development. Our recent analysis of knockout mice of the death effector domain (DED) containing element DEDD-1 has implied an important role of DEDD-1 in tumor progression. We will further determine the involvement of DEDD-1 in tumorigenesis in the context of apoptosis as well as of other potential machineries. We will also study the function of a similar molecule DEDD-2 both *in vivo* and *in vitro*. These studies will not only provide a novel insight into the influence of apoptosis in tumorigenesis, but also suggest a potentiality of tumor manipulation by modulating expression of DEDD molecules.

4. Towards the development of a definitive therapy for Propionic Acidemia.

Propionic acidemia (PA) is the most frequent inborn error of organic acid metabolism in humans. It is caused by a deficiency of propionyl-CoA carboxylase (PCC), which results in accumulation of toxic propionic acid, leading to furious acceleration of ketoacidosis. We generated a mouse model for the severe-type PA by disrupting the PCCA (α -subunit of PCC) gene, and successfully rescued the mice by complementation of a partial PCC-activity restrictedly in the liver or in the skin via a transgene. Having this result, we will establish a novel therapy for PA that is based on an idea of developing "chimeric" organs via transplantation of hepatic stem cells or fibroblast cells into newborns or early infants.

Lab Activities

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

As a daughter series of DBELS, we started a technical lecture series for young scientists. We invite various scientists from not only universities but also research institutes or industries.

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

As an opening ceremony of our lab, we invited Maestro Christian Zimerman (Pianist), for a concert by him, and a discussion (with Prof. Miyazaki) on Music and Science, at the Yasuda memorial auditorium (June 2006). More than 800 audiences have participated.

Visiting Professors

So far, Profs. Edward K. Wakeland (Univ. of Texas Southwestern Medical Center at Dallas) (2007), Diane Mathis and Christophe Benoist (Harvard Univ. Medical School) (2008) visited our lab for 3 months, and had many activities.

Publications

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Laboratory of Structural Physiology

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Introduction and Organization

The Center for Disease Biology and Integrative Medicine (CDBIM) has been established in 2003, and elected Dr. Kasai as the professor of the Division of Basic Medical Sciences (2) of CDBIM in July of 2004. Dr. Kasai was in the National Institute for Physiological Sciences, and officially took office in the University of Tokyo in November, 2005. The Kasai laboratory has moved to the first building of Faculty of Medicine in January, 2006. It belongs to the Section of Functional Biology in the Graduate School of Medicine. Its name has been changed from Division of Biophysics to Laboratory of Structural Physiology in the April, 2008.

Teaching activities

We have 6 doctor and 2 master course students in 2010. We were also involved in undergraduate education of Physiology. In particular, we were responsible for the lectures and student experiments of endocrine physiology.

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 three representative works of this year in some detail.

1) Two-color, two-photon uncaging of glutamate and GABA.

Two-photon microscopy has recently revolutionized the biological sciences. In particular, two features are proving to be very useful when compared with normal excitation modalities, namely imaging fluorescent signals from deep within living tissue and localized photochemical release of caged compounds. The non-linear nature of two-photon excitation provides both of these benefits. Effective two-photon uncaging is predicated upon several chemical properties of the photosensitive probe. Nitroindolyl-caged glutamates have been used by many laboratories for two-photon uncaging experiments, implying such cages can be used with non-toxic photon fluxes. These probes are photolyzed in the 710–730 nm range such that the response at a spine head to the uncaged glutamate appears like single vesicle secretion.

We have here developed a method for bimodal control of neuronal membrane potential with subcellular resolution using optically independent two-photon uncaging of glutamate at 720 nm and GABA at 830 nm. Two-color, two-photon uncaging allowed action potentials from rat hippocampal CA1 neurons to be fired and blocked with the two wavelengths of light. Two-color, two-photon uncaging may enable optically independent control of many other symbiotic chemical messenger pairs (Ref. 1).

2) Simultaneous two-photon activation of presynaptic cells and calcium imaging in postsynaptic dendritic spines.

Dendritic spines of pyramidal neurons are distributed along the complicated structure of the dendritic branches and possess a variety of morphologies associated with synaptic strength. The location and structure of dendritic spines determine the extent of synaptic input integration in the postsynaptic neuron. However, how spine location or size relates to the position of innervating presynaptic cells is not yet known. This report describes a new method that represents a first step toward addressing this issue. The technique combines two-photon uncaging of glutamate over a broad area ($\sim 500 \times 250 \times 100 \mu\text{m}$) with two-photon calcium

imaging in a narrow region ($\sim 50 \times 10 \times 1 \mu\text{m}$). The former was used for systematic activation of layer 2/3 pyramidal cells in the rat motor cortex, while the latter was used to detect the dendritic spines of layer 5 pyramidal cells that were innervated by some of the photoactivated cells. This technique allowed identification of various sizes of innervated spine located $<140 \mu\text{m}$ laterally from the postsynaptic soma. Spines distal to their parent soma were preferentially innervated by cells on the ipsilateral side. No cluster of neurons innervating the same dendritic branch was detected. This new method will be a powerful tool for clarifying the microarchitecture of synaptic connections (Ref. 6).

3) SNARE conformational changes that prepare vesicles for exocytosis.

When cells release hormones and neurotransmitters through exocytosis, cytosolic Ca^{2+} triggers the fusion of secretory vesicles with the plasma membrane. It is well known that this fusion requires assembly of a SNARE protein complex. However, the timing of SNARE assembly relative to vesicle fusion—essential for understanding exocytosis—has not been demonstrated. To investigate this timing, we constructed a probe that detects the assembly of two plasma-membrane SNAREs, SNAP25 and syntaxin-1A, through fluorescence resonance energy transfer (FRET). With two-photon imaging, we simultaneously measured FRET signals and insulin exocytosis in beta cells from the pancreatic islet of Langerhans. In some regions of the cell we found that the SNARE complex was preassembled, which enabled rapid exocytosis. In other regions, SNARE assembly followed Ca^{2+} influx, and exocytosis was slower. Thus, SNARE proteins exist in multiple, stable preparatory configurations, from which Ca^{2+} may trigger exocytosis through distinct mechanisms and with distinct kinetics. (Ref. 4).

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Laboratory of Regenerative Medical Engineering

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Introduction and Organization

The Division is composed of two laboratories, Ushida laboratory and Sakai Laboratory. The Division tightly collaborates with Faculty of Engineering. Prof. Ushida is also charged at Department of Mechanical Engineering, where the laboratory members include Assistant Professor, two Associates and 15 graduate students (as of April 1, 2004). Prof. Sakai also holds a position in Institute of Industrial Science (IIS), University of Tokyo. The current laboratory members at IIS (as of April 1, 2004) include one research associate, one JSPS postdoctoral fellow, one technical assistant, and six graduate students from Department of Chemical System Engineering, Graduate School of Engineering. In addition, four graduate students who belong to other universities do research in our laboratory.

Teaching activities

Prof. Ushida 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. Ushida has also lectures on tissue engineering, advanced biomaterials and biomechanics at Graduate

School of Engineering. Prof. Ito gives a lecture concerning biosystem engineering at the Chemical System Engineering course and Bioengineering course at Graduate School of Engineering School.

Research activities

Prof. Ushida's laboratory aims to establish key technologies for regenerative medicine. One of the projects of our research targets the hard tissue regeneration, such as cartilage or bone by tissue engineering technology. Hard tissue engineering requires the control of its shape in addition to the cell accumulation and scaffold play a key role in meeting this requirement. We focus on the development of biocompatible materials such as synthetic polymer or inorganic materials combined with stem cell biotechnology. Secondly, we try to elucidate mechanisms of cellular responses to physical stimulations such as hydrostatic pressure, shear stress, stretch, through observing intracellular signaling, and to adopt those effects to tissue engineering.

1) Tissue engineering of cartilage or bone defect

- Design and development of biocompatible materials for cartilage or bone using synthetic polymer, inorganic materials or those combination.
- Development of osteoinductive biomaterials hybridized with bioactive substances.

- Order made shaping of scaffolds by router system according to the graphical images of tissue defects
- Establishment of vascular rich graft bed by biomaterials that spur new blood vessel growth.

2) Cellular signal transduction induced by physical stimulations

- Hydrostatic pressure loading to chondrocytes or articular cartilage
- Shear stress loading to endothelial cells
- Stretch loading to endothelial cells, smooth muscle cells

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 biomaterials which can be utilized in peritoneum and future smart biomaterials which can autonomously respond to biological signals. We also study process engineering of the system composed of cells and biomaterials for the progress of tissue engineering.

1) *In situ* crosslinked hydrogels

- Development of novel *in situ* crosslinked hydrogels for a medical use
- Application of the hydrogels for peritoneal adhesion and peritoneal dissemination
- Application of the hydrogels for scaffolds

2) Molecular recognition smart biomaterials

- Development of membranes and micelles in response to a specific ion signal
- Development of a new synthesis way of glycol nucleic acid via a ring opening polymerization
- Application of the smart biomaterials for drug delivery

3) Process design of tissue regeneration

- Mathematical understanding and process design of tissue regeneration in materials *in vitro* and *in vivo*,

especially using the hybrid model of cell automaton and partial differential equations.

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Introduction and Organization

Division of Clinical Biotechnology in The Center for Disease Biology and Integrative Medicine (CDBIM) was established in April 2003. This Division wishes to contribute to the realization of nanomedicine. We actively collaborate and have an interchange of graduate students with Graduate Schools of Engineering & Medicine at The University of Tokyo and Division of Tissue Engineering at The University of Tokyo Hospital. Our division also plays a major role in the Global COE (GCOE) program, which started in 2008, as a novel medicine-engineering interdisciplinary program, and tries to contribute to the production of medical ventures by promoting liaison with the industrial sector and to the production of professionals who understand both advanced medicine and nanotechnology. The division consists of one professor, one research associate professor, one research associate professor, one assistant professor and several project staff members.

Our division focuses on the realization of nanomedicine. Nanotechnology, which has recently been attracting tremendous attention as a leading

scientific field in the 21st century, attempts to process and assemble materials with precision at the atomic/molecular level to produce units with sophisticated functions. Nanodevices produced by nanotechnology integrate materials and systems on a nanometer scale, and hold the key to realizing the futuristic medical system that can serve the needed function at the right time and the right place with minimal invasiveness. Furthermore, nanodevices are expected to become an important interface between basic biomedical science and clinical medicine by facilitating the translation of basic achievements into clinical applications. Our division wishes to produce revolutionary medical nanodevices based on nanotechnology and thereby to spread the idea of "Nanomedicine" intranationally and internationally.

Teaching activities

Traditional medicine-engineering interdisciplinary programs have focused on the exchange of researchers and the promotion of collaborative researches between these two different academic areas. However, the next generation medicine such as "minimum-invasive

diagnosis-treatment" and "targeting medical treatment" and nanotechnologies are developing so quickly with increasing complexity that scholars in both areas find it hard to understand each other. For this reason, it is becoming increasingly difficult for medical doctors to locate technological seeds meeting their medical needs and for engineers to find ways of applying their technological seeds to corresponding medical needs. This situation prevents the effective development of revolutionary medical diagnostical and therapeutic inventions. Division of Clinical Biotechnology intends to create an optimal milieu where undergraduate and graduate students from the medical and engineering fields can respect each other's background, ignores the boundary and study the fusion area in order to achieve the common goal of developing intelligent nanodevices for the futuristic medical system.

Research activities

Drug delivery to the targeted site is strongly desired to enhance the drug function and minimize the side effects. In this regard, drug delivery systems based on self-assemblies of block copolymers (i.e., polymeric micelles) recently draw much attention as one of the medical applications of the nanotechnology. Block copolymers spontaneously form polymeric micelles, which are characterized by the core-shell structure and the size of ~100 nm, in aqueous media. The core of the micelles behaves as a nanoreservoir for drugs, while the coronal shell providing the biocompatible surface. Polymeric micelles can incorporate a variety of drugs including hydrophobic drugs, metal complex drugs, and macromolecular drugs such as proteins and DNA, and release them in a sustained manner or in response to environmental changes such as pH. The site-specific drug delivery can be achieved by conjugation of the pilot molecules on the surface of polymeric micelles. Thus, polymeric micelles behave as intelligent chemical nanomachines for the drug targeting.

The long-circulation of drug carriers is a requisite for the successful drug targeting. The main obstacles to long-circulation are considered to be glomerular excretion in the kidney and recognition by the reticuloendothelial system (RES) located at the liver,

spleen and lung. Polymeric micelles can escape from those barriers in the body, resulting in stable blood circulation. Another advantage of using polymeric micelles is their preferential accumulation in solid tumors, which might be due to microvascular hyperpermeability and immature lymphatic system in tumor tissues. We have succeeded in the tumor-selective delivery of several antitumor drugs including adriamycin (ADR), cisplatin (CDDP) and oxaliplatin by polymeric micelles, and observed enhanced antitumor activity with reduced side effects. These micellar formulations are currently being tested in clinical trials.

Recently, plasmid DNA (pDNA) and siRNA are receiving much attention as promising tools for the treatment of genetic and intractable diseases. One of the major requirements for therapeutic use of pDNA and siRNA is the development of gene vectors, which can safely and effectively deliver them into specific cells and regulate their expressions. Recently, we have prepared polymeric micelles incorporating pDNA through the electrostatic interaction between DNA and positively charged block copolymers. The polymeric micelles protected the loaded DNA from degradation by nuclease attack and showed efficient gene transfer to a variety of cells. Also, various smart functions such as the targeting ability and environmental sensitivity can be integrated with polymeric micelles, offering the opportunities to develop effective synthetic vectors resembling viral functions. Thus, polymeric micelles are expected as useful nanocarriers of pDNA and siRNA for in vivo use.

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Laboratory of Environmental Health Sciences

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Introduction and Organization

Laboratory of Environmental Health Sciences is a laboratory established as a part of the Center for Disease Biology and Integrative medicine in 2005. Since then the of the laboratory was markedly expanded to comprise of as many as 30 members, including postdoctoral fellows, graduate and undergraduate students. Dr. Chiharu Tohyama was given Achievement Award from the Japanese Society of Hygiene in May 2010 for the accomplishment of his research in toxicology and environmental health. .

Research activities

Children's health problems of today include such conditions as disorders in the reproductive and immune functions, learning deficits, mental problem and 'metabolic syndrome'. Our research is carried out on the recognition that the homeostasis is disrupted by various environmentally hazardous chemicals, to which expectant mothers and their newborn babies are exposed during their highly sensitive period of life, and that the contamination with these chemicals may lead to various disease conditions in children after

birth. Our experimental investigations are focused on the epigenetic mechanisms that alter the susceptibility to chemicals, effects of chemicals on the learning and emotion and the identification of molecular target of chemicals. Our research efforts are further directed to develop methodologies for evaluating behavioral toxicities *in vivo* and to establish *in vitro* toxicity techniques at cellular and molecular levels. In addition to these basic approaches to the environmental toxicology, we aim to provide data for obtaining the safety standard in environmental factors and food, and to contribute to the development of research in life and clinical sciences. Among a variety of potentially toxic substances in the environment, we focus especially on dioxin and its related-compounds and heavy metals which react with specific receptors and proteins.

The primary goal of the Laboratory's research program is to elucidate toxicity mechanisms for various environmentally hazardous chemicals. To achieve this goal, 'forward and reverse toxicology' approaches are used to determine how adverse responses of laboratory animals, which are used as an experimental substitute for humans, to a particular chemical are similar to or different from the adverse

responses of humans.

The outcomes of our research provide not only fundamental information for human health risk assessment that can lead to the establishment of adequate margins of safety for human exposure to environmental chemicals. They give the general public a greater sense of security in their surroundings and they provide clinical medicine and the basic life sciences new knowledge that is human health relevant.

Laboratory's Research Themes

1. Elucidation of mechanisms involved in the manifestation of toxicity at the molecular and cellular level due to exposure to environmental pollutants, such as dioxin/PCBs and heavy metals.
2. Clarification of epigenetic mechanisms that alter susceptibility to environmental chemicals.
3. Development of methodologies for evaluating the toxicity of chemicals to the learning and emotion of rodents and of *in vitro* toxicity techniques at the molecular and cellular levels.
4. Development and application of techniques and methodology for evaluating risks of toxic substances in formulating safety standard for the environment and food.

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 in the future and to give a toxicology and environmental health courses for graduate and undergraduate students. This laboratory is actively involved in these tasks. The Laboratory will be responsible for full a credit course on 'Principles and Applications of Environmental Health Sciences'. In addition, several lectures are given to undergraduate students at School of Medicine and School of Health Sciences and Nursing. From 2008 this laboratory has become a member of a Global COE project, 'Medical system innovation'.

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Laboratory of Animal Resources

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Introduction and Organization

Our laboratory was established as the Division of Animal Research affiliated with the Faculty of Medicine in April 1971. The building for animal experimentation was completed and the accommodation and experimentation of laboratory animals started in 1973. In 2003, the laboratory was reorganized as the Section of Animal Research of the Center for Disease Biology and Integrative Medicine (CDBIM). In 2008, the Laboratory of Animal Resources was established to strengthen research activities in addition to the Section of Animal Resources.

The members of our laboratory and section are 4 teaching staffs, 3 technical support staffs, an assistant manager of CDBIM, an administrative staff, a teaching assistant, 8 assistant laboratory animal technicians, and 4 assistant clerks. In addition, about 10 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, and mice. The number of registered users of our facility was 378 at the end of academic year 2010.

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 Animal Care and the Use Committee of Graduate School of Medicine, the

University of Tokyo (IACUC). The committee (Chair, Prof. Hiroki Kurihara) reviews the plans of animal experimentation and help 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 School 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.

1. Generation of hyperactive mTOR transgenic mice

mTOR is a highly conserved serine/threonine kinase that regulates a broad range of cellular functions in cell growth. mTOR forms two functionally distinct complexes, mTOR complex 1 (mTORC1) and mTORC2. mTORC1 contains raptor and mLst8, whereas mTORC2 contains rictor, mSin1, and mLst8. The hyperactive mTOR mutant shows enhanced kinase activity and activates the mTORC1 pathway strongly and chronically in cultured cells. We generated transgenic mice which express a hyperactive mTOR mutant in forebrain and cerebellar Purkinje cells. We observed the some of the neurons in mTOR transgenic mice were enlarged presumably due to activation of mTOR1 pathway. We are currently investigating molecular mechanisms underlying the phenotypes of mTOR transgenic mice.

2. Genetic approaches to cerebellar function using metabotropic glutamate receptor subtype-1 (mGluR1) transgenic mice

We previously demonstrated that mGluR1 knockout showed ataxic gait, deficient long-term depression and impaired synapse elimination. These phenotypes were rescued by expression of an mGluR1 transgene with Purkinje cell-specific promoter (mGluR1-rescue mice). However, the role of mGluR1 in the adult mice remains elusive, mainly due to lack of conventional and reproducible method to block mGluR1 expression at a certain developmental stage. We established an mGluR1 conditional knockout (cKO) mice by using the tetracycline-controlled gene expression system to understand roles of mGluR1 in adult brain. The mGluR1 cKO mice express mGluR1 only in Purkinje cells and its expression can be controlled with oral administration of a tetracycline analog, doxycycline. We found that suppression of the mGluR1 expression in the adult mGluR1 cKO mice led to ataxic gait and impaired motor coordination, suggesting that mGluR1 is essential for cerebellar function in mice not only during postnatal development but also in adulthood.

3. Role of mGluR1 in classical eyeblink conditioning

Classical eyeblink conditioning is common to humans and other mammals such as rabbits and mice,

and has been a valuable paradigm for the study of associative motor learning as well as human neurological disorders. Eyeblink conditioning procedure consists of a conditioned stimulus (CS) and a blink-eliciting unconditioned stimulus (US). Naive animals initially exhibit unconditioned response (UR) following US onset. After repeated trials of conditioning with a pair of CS-US, they come to associate CS and US and to exhibit conditioned response (CR) before the US onset. Our previous studies using mGluR1 knockout mice showed that mGluR1 in cerebellar Purkinje cell is required for delay paradigm of eyeblink conditioning. We trained the mGluR1 cKO mice in eyeblink conditioning before or after doxycycline administration to determine which learning process requires mGluR1 function.

4. Study of obese mice

We generated mutant mice in which a histone H2B-KikGR fusion gene is introduced into the ROSA26 locus by homologous recombination using ES cells. Homozygous knock-in (R26-H2B-Kik-GR/H2B-Kik-GR) mice died around 4 weeks after birth. Heterozygous (R26-H2B-Kik-GR/+) mice are not lethal and develop obesity. Body weights of R26-H2B-Kik-GR/+ mice remarkably increased in comparison with control mice at the age of 6 weeks. Leptin and insulin levels in serum of R26-H2B-Kik-GR/+ mice were significantly higher than those of control mice, while glucose level in R26-H2B-Kik-GR/+ mice was not significantly changed. We also found that vacuolation of hepatocyte in liver, hypertrophy of brown adipocytes and white adipocytes, hypertrophy of acinar cells and islet cells in pancreas, hyperplasia of lymphocytes in thymus. These results suggest the possibility that R26-H2B-Kik-GR/+ mice are new model animals for obesity.

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Laboratory of Molecular Radiology

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Introduction and Organization

This laboratory was renamed as the Laboratory of Molecular Radiology in 2008 to strengthen research activities. The main duty to support the use of radioisotope at Graduate School of Medicine has been also continued. Historically, in 2003, the Department of Radiation Oncology and the Radiation Research Institute were joined to form a new department.

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 department. There is no remarkable change in the maintenance system and frequency of the use of radioisotope this year.

Teaching activities

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. After that, 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 casualty medicine is included in this new course. Even though radiation casualty is rare, all clinicians should know how to treat patients exposed to radiation.

We also take part in the education of radiation health science for the 3rd year students specialized in health science. Radiation protection is emphasized in this course.

At Graduate School of Medicine, molecular biology of DNA damage response to radiation and DNA repair is more emphasized.

In addition, education courses for users of radioactive materials frequently take place.

Research activities

Before the present professor took the position, a wide range of radiation biology, including biological effects of low-dose irradiation, nonhomologous end joining (NHEJ) for DNA double-strand breaks, apoptosis that responds to DNA damage, and radio-sensitization had been topics in this department. Since 2005, homologous recombinational repair has been the main subject.

RecA in *E. coli* and its homolog Rad51 in budding yeast play a central role in homologous recombinational repair. Historically, mechanism of homologous recombination was extensively studied in these organisms, whereas homologous recombination had been recognized as a minor pathway of DNA double-strand break repair in higher organisms. However, subsequent studies revealed that homologous recombination as well as NHEJ plays an important role in DNA double-strand break repair in higher organisms. There are two major differences between these two pathways. NHEJ functions at any stages of the cell cycle, whereas homologous recombination is restricted to the S to M phases. Another difference is that NHEJ is an error-prone repair pathway and homologous recombination is an error-free repair pathway.

We have been studying on the functions of Rad51 paralogs, which share structural similarity with Rad51. There are five genes that belong to this paralog family in mitotic cells. Although they share structural similarity with each other, there is no functional redundancy. To clarify their roles, we have generated their mutant human cells by gene targeting and RNA interference.

Rad51C, a central component of two protein complexes formed by the members of the Rad51 paralog family, activates DNA repair pathways by responding DNA damage signals through its direct interaction with Rad18. We confirmed that Rad51-dependent homologous recombination is impaired in Rad51C-deficient human cells. Additionally, aberrations of the centrosome, which is essential for correct chromosome segregation, and aneuploidy were found to be increased in the mutant cells. ATR and Chk1, which transmit DNA damage signals, were shown to be responsible for the aberrations, suggesting that the DNA damage signaling pathway plays a causal role in the generation of centrosome aberrations and aneuploidy. Thus, we are studying on Rad51 paralogs from the viewpoint of the maintenance of chromosomal integrity by DNA repair.

In contrast to early stages of homologous recombination, little is known about the mechanisms of homologous recombination at late stages. The Mus81-Eme1 complex has been shown to resolve

recombination intermediates. Subsequent studies revealed that this enzyme plays a role in the resolution of stalled replication forks. We have studied on the function of this complex in human cells. Unexpectedly, the mutant cells are hypersensitive to DNA cross-linking agents rather than to replication inhibitors. Cisplatin and its analogs are widely used in current cancer treatment. Because these drugs induce DNA cross-linking, we are trying to understand the role of Mus81-Eme1 from the viewpoint of cancer therapy.

The impaired recombinational repair pathway is associated with numerous chromosomal aberrations. It is established that some breast cancers arise from defective recombination. It is also possible that other cancers are caused by the similar processes. Furthermore, we hypothesize that non-cancerous diseases can be associated with DNA damage responses. The study on homologous recombination also contributes to the development of radiation therapy. Radiation and DNA-damaging chemotherapeutic agents induce DNA double-strand breaks, 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 will establish the basic science of homologous recombinational repair.

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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 academic year 2010 (April through March).

1. International Educational Exchange

1.1 Student counseling about education and research

In 2010, there were 153 foreign students (39 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 76 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, 20 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 80 people attended in 2010, at the Sanjo Kaikan, a reception hall on the Hongo campus.

The annual Ryugakusei Ronbun Contest was first held in 1999. As in previous years, in the 2010 Contest foreign students gave oral presentations based on their research papers to interested fellow students and faculty, and the five best speakers were given awards.

A formal agreement for academic exchange between the University of Pennsylvania and the

University of Tokyo was renewed in May 2004. Since that time, ten University of Tokyo students have taken research electives at the University of Pennsylvania every year, 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, sixteen University of Tokyo students 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, seven University of Tokyo students have attended clinical electives at the University of Michigan Medical School, and three 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, six University of Tokyo students visited to attend research electives at Munich University, and three 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 University of Washington Medical School in November 2005. Since the start of the program in 2005, six University of Tokyo students have attended clinical electives at the University of Washington Medical School, and one student from the University of Washington Medical School has 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 Taipei Medical University in November 2005. Since the start of the program in 2005, two University of Tokyo students visited to attend clinical electives at Taipei Medical University and six 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 Mahidol University in September 2006. Since the start of the program in 2006, five University of Tokyo students visited to attend research electives at Mahidol University, and seven students from Mahidol University have taken clinical electives at the University of Tokyo.

1.2 Counseling University of Tokyo medical students and researchers about short-term and longer overseas study programs

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. New project (International Training Program)

This project (total budget: 100,000,000 yen/5 years) provides opportunities for young researchers from the Graduate School of Medicine at the University of Tokyo to receive instruction and training at partner institutions in the USA, with the goal of helping them excel not only as scientists, but also as educators for the next generation and as administrators of their research groups.

The details of the plans for the young researchers at the partner institution in USA are as follows.

- (1) They should carry out highly advanced medical research.
- (2) They should observe and experience participatory, student-centered forms of education (tutorials, etc.) used with medical students.
- (3) They should observe and experience the management of research laboratories, particularly with regard to the importance of the activities of graduate students and postdoctoral fellows.
- (4) They should observe how teaching assistants contribute in education and research, and how teaching assistants are trained to become leaders and mentors.

In 2008, six young researchers from the Graduate School of Medicine at the University of Tokyo began studying at the partner institutions in the USA.

3. Education and research

3.1 Education

In 2009, Dr. Green taught a course open to all students in the Graduate School of Medicine: Introduction to Scale Development.

Dr. Green also taught two other graduate-level classes: International Epidemiology 1 and 2.

Mr. Christopher Holmes taught Medical English 1, 2, and 3, the first two of which are required for all medical students. The Office also organized classes in English for the Health Sciences.

In 2009, Dr. Green and Mr. Holmes led ad hoc sessions in Oral Presentation Training. These sessions were open to all students and teaching staff in the Graduate School of Medicine and the Faculty of Medicine.

3.2 References

1. Suzukamo Y, Fukuhara S, Green J, Kosinski M, Gandek B, Ware JE.
Validation testing of a three-component model of Short Form-36 scores.
J Clin Epidemiol. 2011 Mar;64(3):301-8.

Museum of Health and Medicine

Director

Kazuhiko Ohe

Specially-appointed technical expert

Atsushi Kitade

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

History and overview

The origins of the School of Medicine and the University of Tokyo Hospital can be traced back to the establishment of the Kanda Otamaga-Ike Vaccination Center in 1858. In 2008, it celebrated its 150th anniversary. The Museum of Health and Medicine was planned as part of commemorative projects to celebrate the 150th anniversary of the founding of the School and the Hospital, and was opened on January 20, 2011.

One of the themes for the commemorative projects marking the 150th anniversary was the “development of communication between health science and care and society,” and the Museum of Health and Medicine forms one of the pillars of this.

In establishing the Museum of Health and Medicine, we renovated the School of Medicine’s Central Building (Medical Library), which had originally been instituted as part of the commemorative projects celebrating the 100th anniversary of the founding of the School and the Hospital. The Museum has about 400m² areas, including about 70m² of a permanent gallery and 230m² of special exhibition rooms.

The aims of the Museum are to: (1) provide health and medical information to the public, (2) educate medical students and students, (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 medicine 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 is 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 its graduates since the Meiji era (1868-1912), and the latest information about infectious diseases. Furthermore, the exhibition explained current efforts in oral vaccine, virotherapy and the diagnosis and treatment of neglected tropical diseases.

Since the opening of the Museum, more than 8,000 people had visited the first special exhibition up until June 30, 2011. The Museum will continue to plan and organize according to the aforementioned purposes of the Museum.

Overview of operations

The opening hours are 10:00-17:00. 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.

The International Research Center for Medical Education (IRCME)

Director & Professor

Kazuhiko Yamamoto, M.D., Ph.D.

Professor

Kiyoshi Kitamura, M.D., Ph.D.

Lecturer

Hiroataka Onishi, M.D., M.H.P.E.

Lecturer

Hiroshi Nishigori, M.D., M.M.E., Ph.D.

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

History and organization

The University of Tokyo has established International Research Center for Medical Education (IRCME) in 2000. The Ministry of Education (in 2001 reformed to Ministry of Education, Culture, Science and Sports), the University of Tokyo, and the Graduate School of Medicine positioned IRCME as a base for promoting international cooperative studies of medical education. In 2010 IRCME celebrated the 10th anniversary.

IRCME consists of three departments of International Cooperative Study for Medical Education, Planning & Coordination for International Cooperative Projects and Information on Medical Education, and visiting professor from abroad. We hope that the research in medical education carried out by IRCME will improve medical education and health care in many countries.

The mission of IRCME includes research in international cooperation in medical education, research in medical education, and development of human resource in medical education. Promotion of and contribution to education in the Faculty of Medicine, University of Tokyo and University of

Tokyo Hospital is also our fundamental role.

International Cooperative Study in Medical Education

The University of Tokyo, especially the Faculty of Medicine, takes pride in its academic excellence internationally. Compared with other Western distinguished universities, however, activities and research in medical education have been weak for a long time.

To fulfill the mission, faculty and staff in IRCME conduct research on a wide range of topics in undergraduate, postgraduate and continuing medical education. One of our objectives is to establish a center for medical education research in Asian Pacific Area to collaborate with variety of medical education researchers.

IRCME also makes important contributions to undergraduate and postgraduate medical curricula of the Faculty of Medicine, the University of Tokyo directly. As medical education experts, we are giving appropriate information to all the faculty members about teaching and learning in medicine.

Planning & Cooperation for International Cooperative Projects and Information on Medical Education

Department of Planning & Coordination for International Cooperative Projects and Information on Medical Education is responsible for developing international cooperation in health professions education area (medicine, dentistry, pharmacy, nursing, public health, rehabilitation, etc) facilitated by the Ministry of Education, Culture, Sports, Science, and Technology. This department should lead any international cooperation projects in health professions education area in Japan and aim at face-to-face and heart-to-heart international cooperation. Activities are listed below.

1. Japan International Cooperation Agency (JICA) appointed IRCME as the cooperative agency for JICA Medical Education Project, Afghanistan. Currently IRCME is working for the follow-up scheme of the above project. Counterpart of the project has been Ministry of Higher Education and Kabul Medical University. In April 2009 Onishi visited Afghanistan to hold the National Conference for Medical Education in Kabul. In July and November 2009 IRCME accepted 27 faculty members from 7 medical schools in Afghanistan to provide medical education training.
2. JICA entrusted Joint Venture of University of Tokyo and System Science Consultants with the Project for Medical Education and Research for the Setthathirath Hospital, the Lao People's Democratic Republic (2007 Dec-2010 Nov). Kitamura, Nishigori and Onishi visited the hospital to provide trainings and advices to help them establish the national standard of clinical education.
3. IRCME established Collaborating Research Center for Medical Education, University of Tokyo in University of Health Sciences, Lao PDR to promote research in medical education.

Visiting Professors

IRCME invites specialists from abroad with expertise in medical education and international cooperation to be visiting professors. They advise and instruct IRCME on planning and on educational activities, and collaborate with IRCME faculty and staff on educational research.

Through IRCME-sponsored lectures and seminars, they also provide intellectual stimulation to medical students, interns, and residents, and introduce new information on medical education and international cooperation to a wider audience.

In 2010, we welcomed two visiting professors:

- Dr. Graham McMahon (21 Sep – 16 Dec, 2010), Assistant Professor of Medicine, Harvard University, USA
- Dr. Gominda Ponnampuruma (7 Feb – 18 March, 2011), Senior Lecturer, Department of Medical Education, Colombo University, Sri Lanka.

They offered several seminars, lectures for international trainees, and many suggestions to IRCME.