

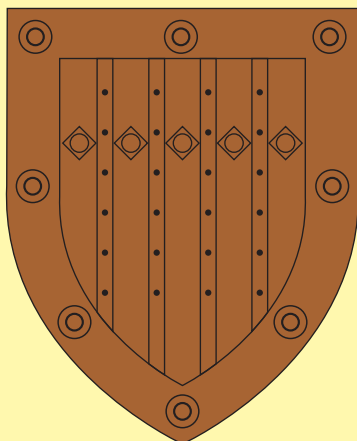
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ANNUAL REPORT OF
THE GRADUATE SCHOOL OF MEDICINE
AND
THE FACULTY OF MEDICINE
THE UNIVERSITY OF TOKYO
REPORTS FOR THE PERIOD April 2008 — March 2009



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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 2008-March 2009

Introduction

This is the report of the University of Tokyo's Faculty of Medicine and Graduate School of Medicine for the years 2008. Here we document each department's research and education activities.

The University of Tokyo has a historically unique role as the leading force in medicine within Japan. It is only natural to expect that we will also be in the forefront of medicine worldwide. We take it as our mission to be an internationally recognized source of important research results, and a center for training outstanding medical scientists and clinicians.

In the 20th century, medicine was dominated by the West, but we are confident that in the 21st century much greater contributions will come from Asia. In that context the role of Japan, and in particular that of the Graduate School of Medicine at the University of Tokyo, will become even more important. Always conscious of our mission, we should continue pursuing our educational and scientific interests enthusiastically.

As we create the future, let us strive to achieve the best in medical research and teaching, and to provide the best possible clinical care.

Takao Shimizu

Dean, Faculty of medicine and Graduate School of Medicine

The University of Tokyo

March, 2009

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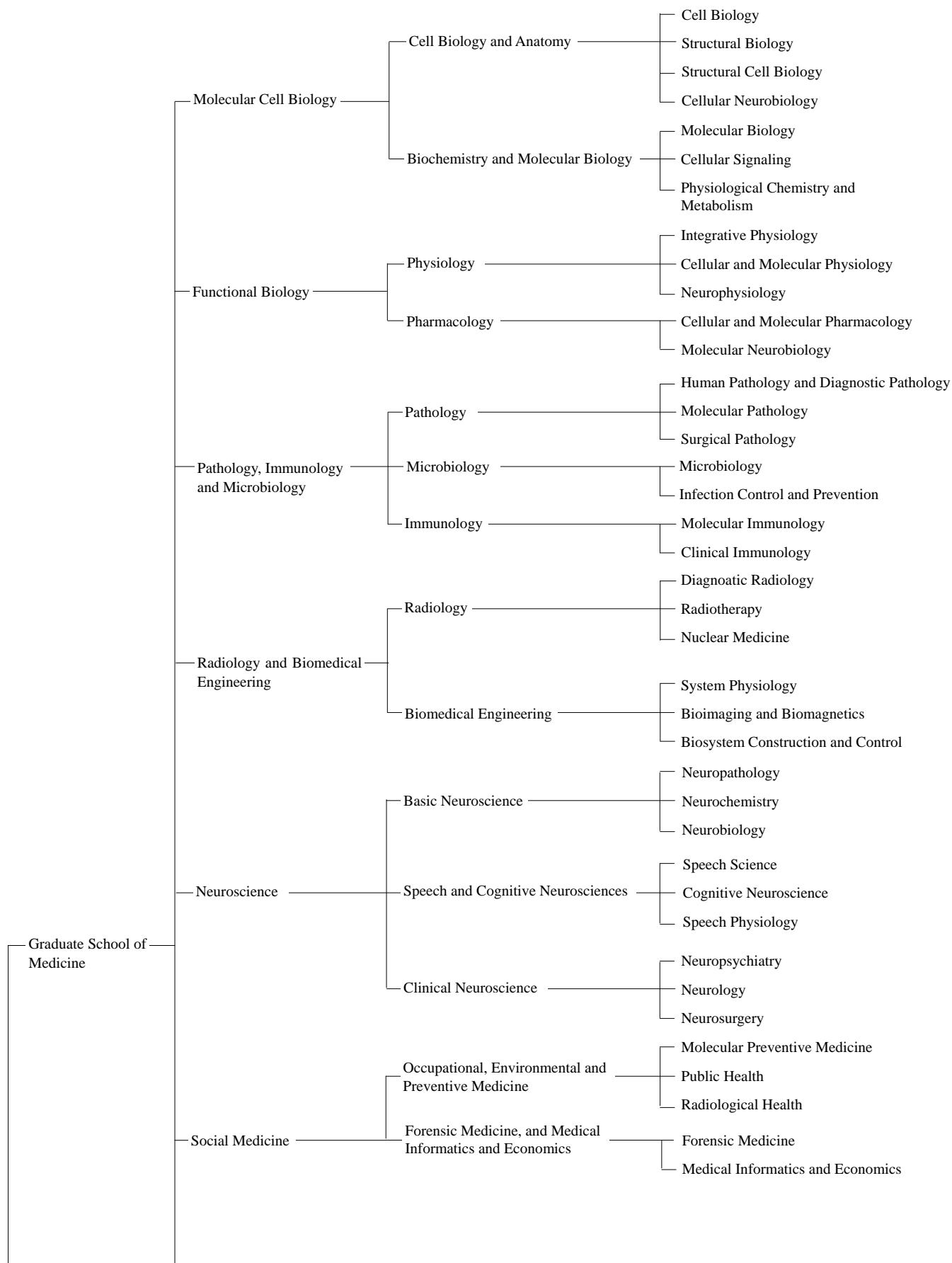
History

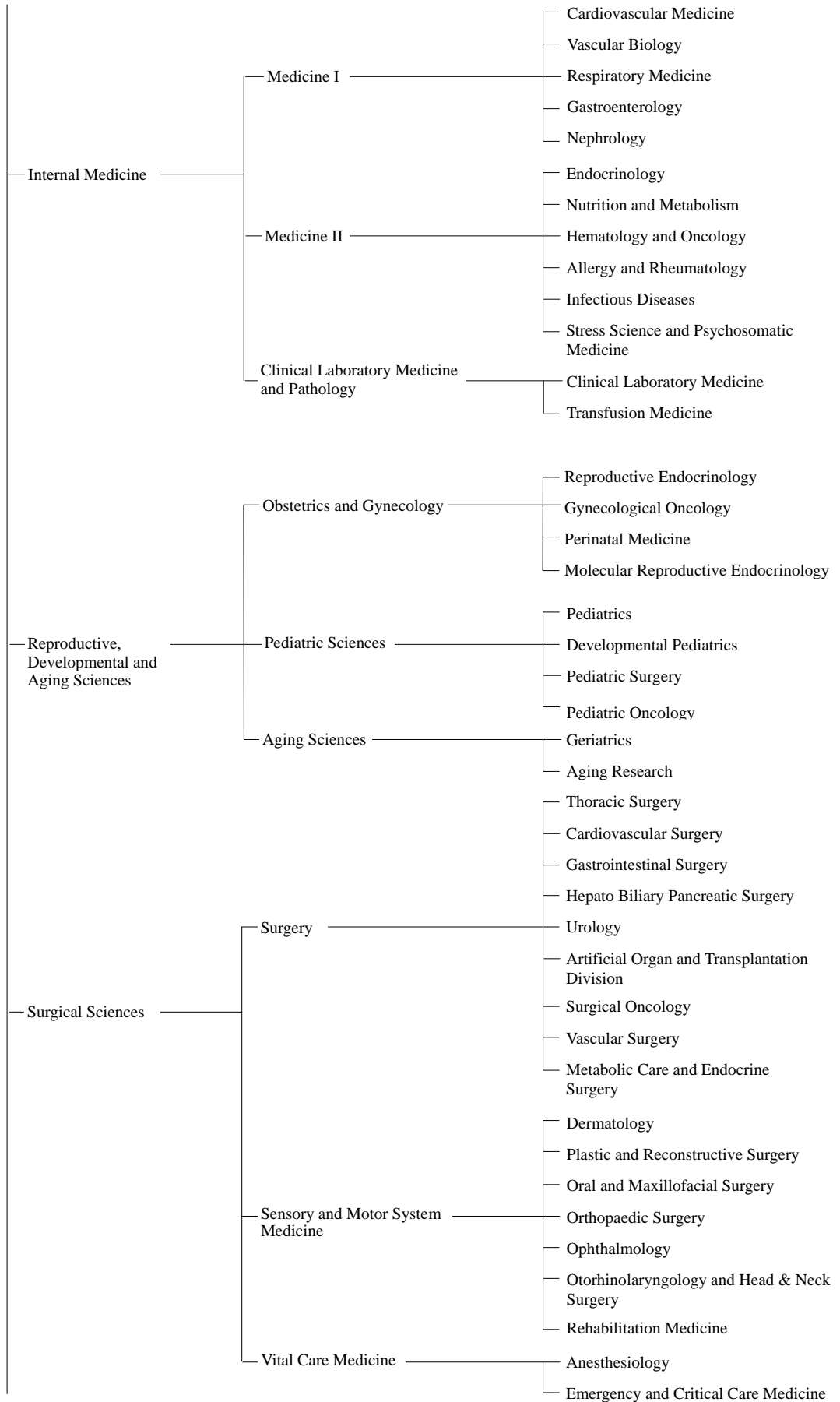
- 1858 May. 82 practitioners trained in Dutch (European) medicine in Edo (Tokyo) laid out money and established at Kanda Mitamagaike Vaccination station called the Shutojyo (vaccination center).
 Nov. The Shutojyo burned by a fire which emerged from Kanda Aioicho, continued its operation at othersites such as a residence of Ito Genboku.
- 1859 Sep. The Shutojyo was moved to and reconstructed at Shitaya Izumibashi Dohri.
- 1860 Oct. The Shutojyo became an official medical institution of the Shogunate Government.
- 1861 Oct. The Shutojyo was renamed as Seiyo Igaku-syo (Institute of Western Medicine) and offered courses of Western medicine in the fields of education, autopsy, and vaccination.
- 1863 Feb. The Seiyo Igaku-sho was renamed as Igaku-sho (Institute of Medicine).
- 1868 Jul. The Igaku-sho, affiliated with the Military hospital which was moved from Yokohama to Todo residence in Shitaya, was renamed as Daibyoin (the Great Hospital).
- 1869 Feb. The Daibyoin renamed as Igakko-ken-byoin (Medical School and Hospital).
 Dec. Igakko-ken-byoin was renamed as Daigaku-Higashiko (University East Building).
- 1871 Jul. Ministry of Education was established and Daigaku-Higashiko was renamed as Higashiko (East Building).
- 1872 Aug. School System was established, renaming Higashiko as Daiichi-daigaku-ku-igakko (The 1st 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, 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 University of Tokyo Faculty of Medicine renamed as Imperial University Medical college. Graduate School was established.
- 1897 Jun. The Imperial University was renamed as Tokyo Imperial University.
- 1917 Aug. Eiraku Hospital affiliated with Ministry of Education Medical Practice License Examination, moved to Tokyo Imperial University and renamed as Koishikawa hospital affiliated to Tokyo Imperial University Medical College.
- 1919 Apr. Faculty system was established renaming Medical College as Faculty of Medicine.
- 1931 Feb. The first building of the Faculty of Medicine was constructed.
- 1936 Jan. Brain research office donated by Mr. Horikoshi Hisasaburo.
 Nov. The second building of the Faculty of Medicine (main building) was constructed.
- 1947 Oct. Tokyo Imperial University renamed as The University of Tokyo.
- 1950 Apr. Institute of Nursing renamed as University Nursing School.
- 1953 Apr. School of Health Care and Nursing founded.
 Jul. Graduate School of the new system founded, Division of Biological Science Dr. Med. of Medicine.
- 1956 Apr. Midwives School established.

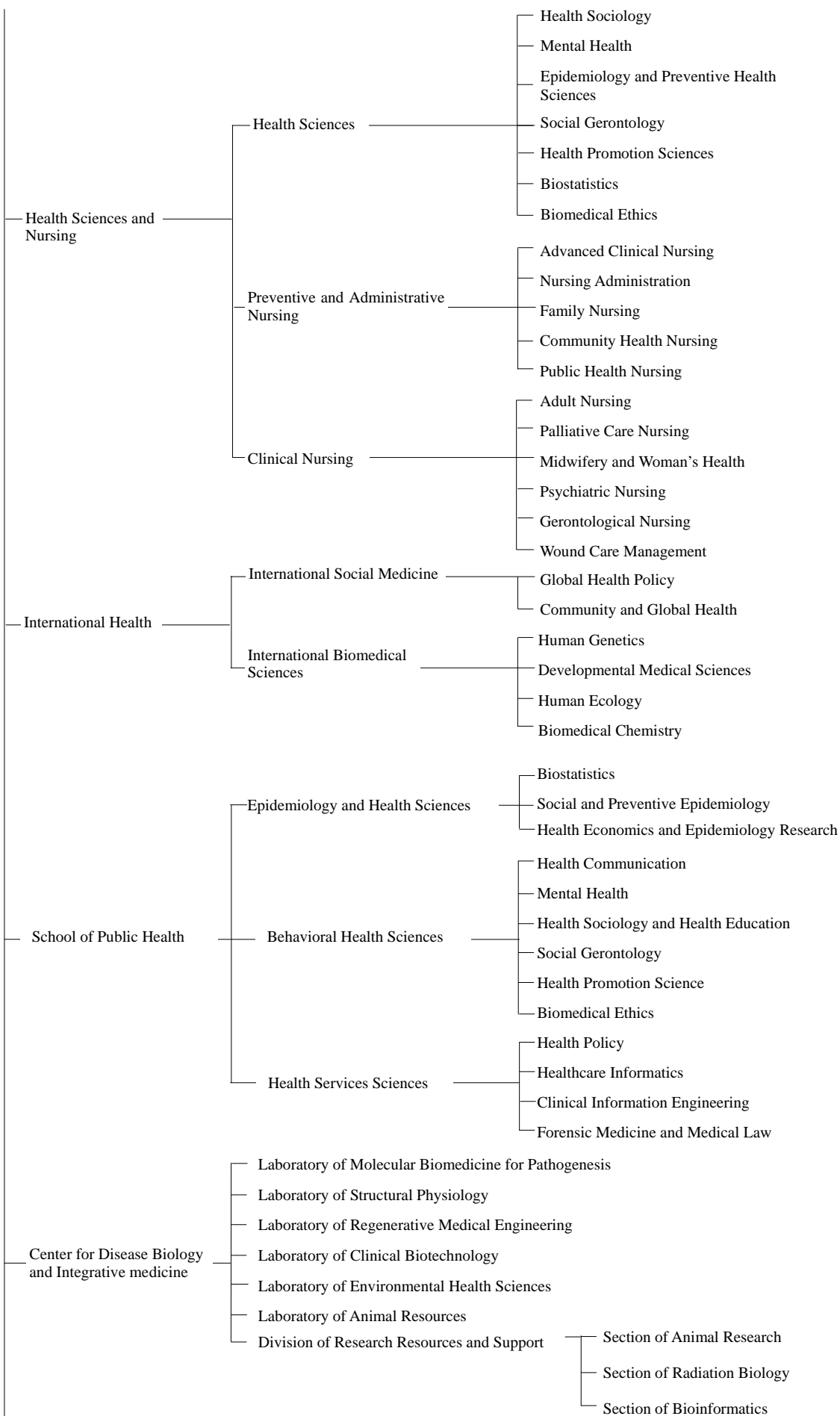
- 1958 Apr. Division of Pharmaceutical Sciences became independent Faculty.
 May. Celebrated centennial of The University of Tokyo Faculty of Medicine.
- 1961 Mar. Medical Library was built in memorial of the centenary.
 Apr. Institute of Medical Electronics established.
- 1965 Apr. Research Institute of Logopedics and Poniiatrics was established.
 School of Health Care and Nursing reorganized as the School of Health Sciences.
 Graduate School of The University of Tokyo Reorganized and Division of Biological Science.
 Dr.Med. Science course became Medical Science Division.
 Health Science Course was established in Medical Science Division.
- 1966 Sep. The third building of Faculty of Medicine was constructed.
- 1971 Apr. Laboratory for Animal Experiments was established.
- 1973 Mar. Animal Center for Biomedical Research was constructed.
- 1983 Jan. Annex of the third building of the Faculty of Medicine was constructed.
- 1985 Sep. Medical and International Academic Affairs established.
- 1987 Apr. Graduate School specialized course was changed to major.
- 1992 Apr. School of Health Sciences became The School of Health Science and Nursing.
 School of International Health was established in Medical Science Division.
 Jul. Radiation Research Institute was established.
- 1995 Apr. As the result of the shift to the chair system of the Graduate School of Medicine, four divisions were abolished, Third Basic Medicine, Social Medicine, Third Clinical Medicine and Fourth Clinical Medicine. Instead, four divisions were established, Pathology, Immunology and Microbiology, Social Medicine, Reproductive, Developmental and Aging Science and Surgery.
- 1996 Apr. As the result of the shift to the chair system of the Graduate School of Medicine, three divisions were abolished, First Clinical Medicine, Health Science and International Health. Instead, three divisions were established, Internal Medicine, Health Science and Nursing and International Health.
- 1997 Apr. As the result of the shift to the chair system of the Graduate School of Medicine, three divisions were abolished, First Basic Medicine, Second Basic Medicine and Second Clinical Medicine. Instead four divisions were established. Molecular Cell Biology, Functional Biology, Radiology and Biomedical Engineering and Neuroscience.
 As the result of above mentioned reorganization, three institutes were abolished, Institute of Brain Research, Institute of Medical Electronics and Institute of Logopedics and Phoniatics.
- 1999 Apr. Master Course of Medical Science was established in 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.
 (The shared facility for education and research)
- 2001 Apr. University Branch Hospital was united to 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 Tokyo was renamed the University of Tokyo National University Corporation.
- 2007 Apr. The School of Public Health was established. This school offers programs for Master public Health.
- 2008 May. The University of Tokyo Faculty of Medicine and the University of Tokyo Hospital celebrated their 150th anniversary.

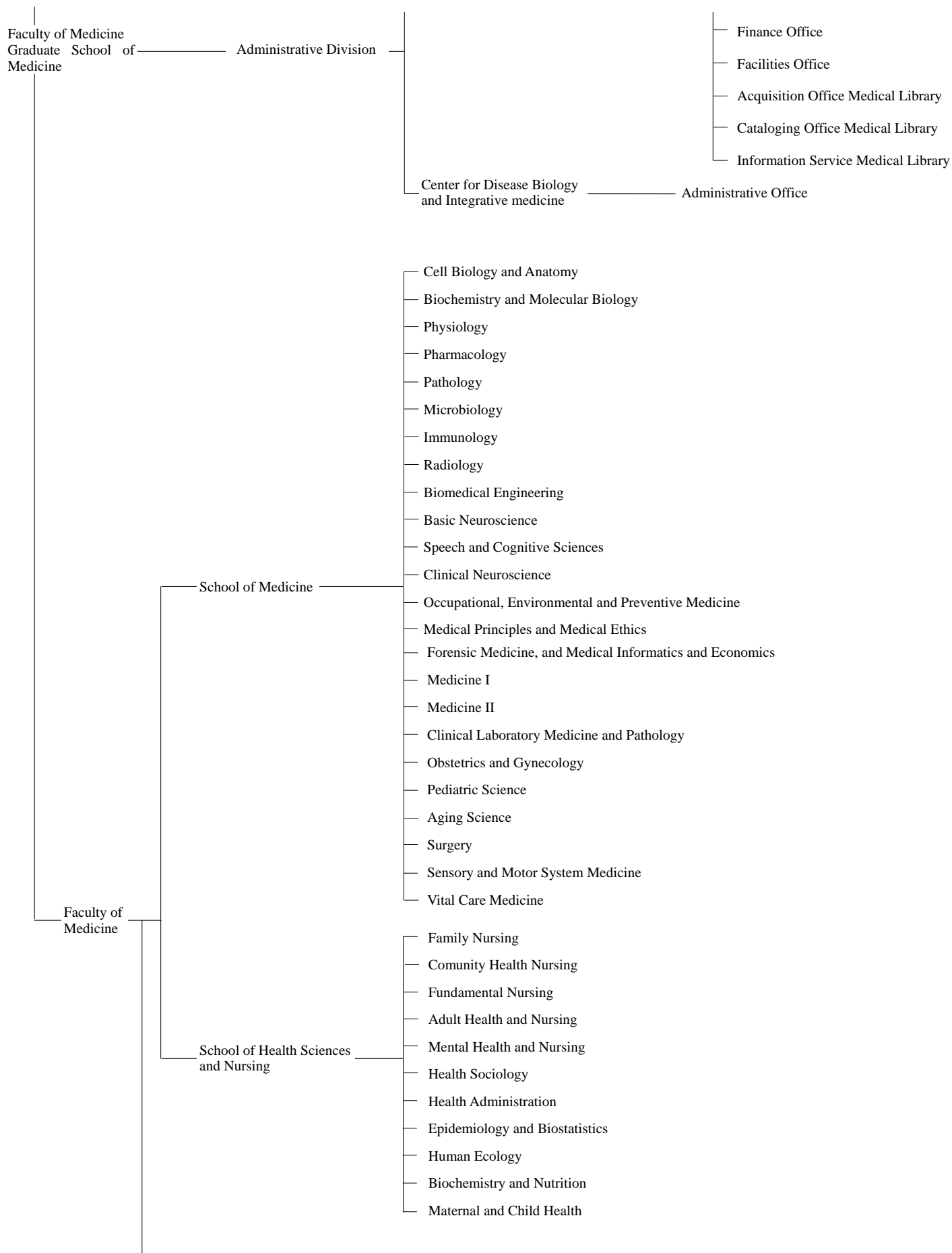
Organization Chart

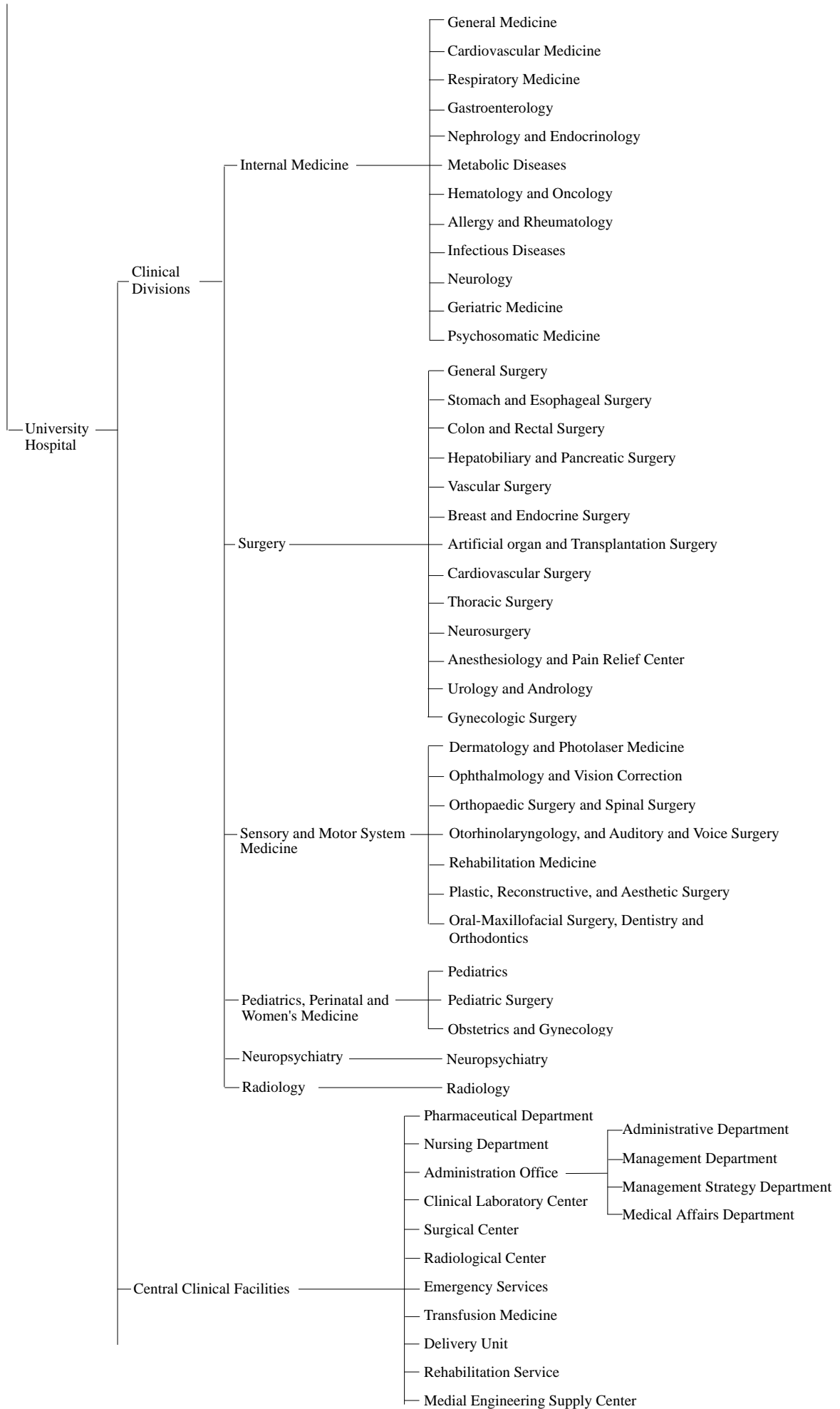


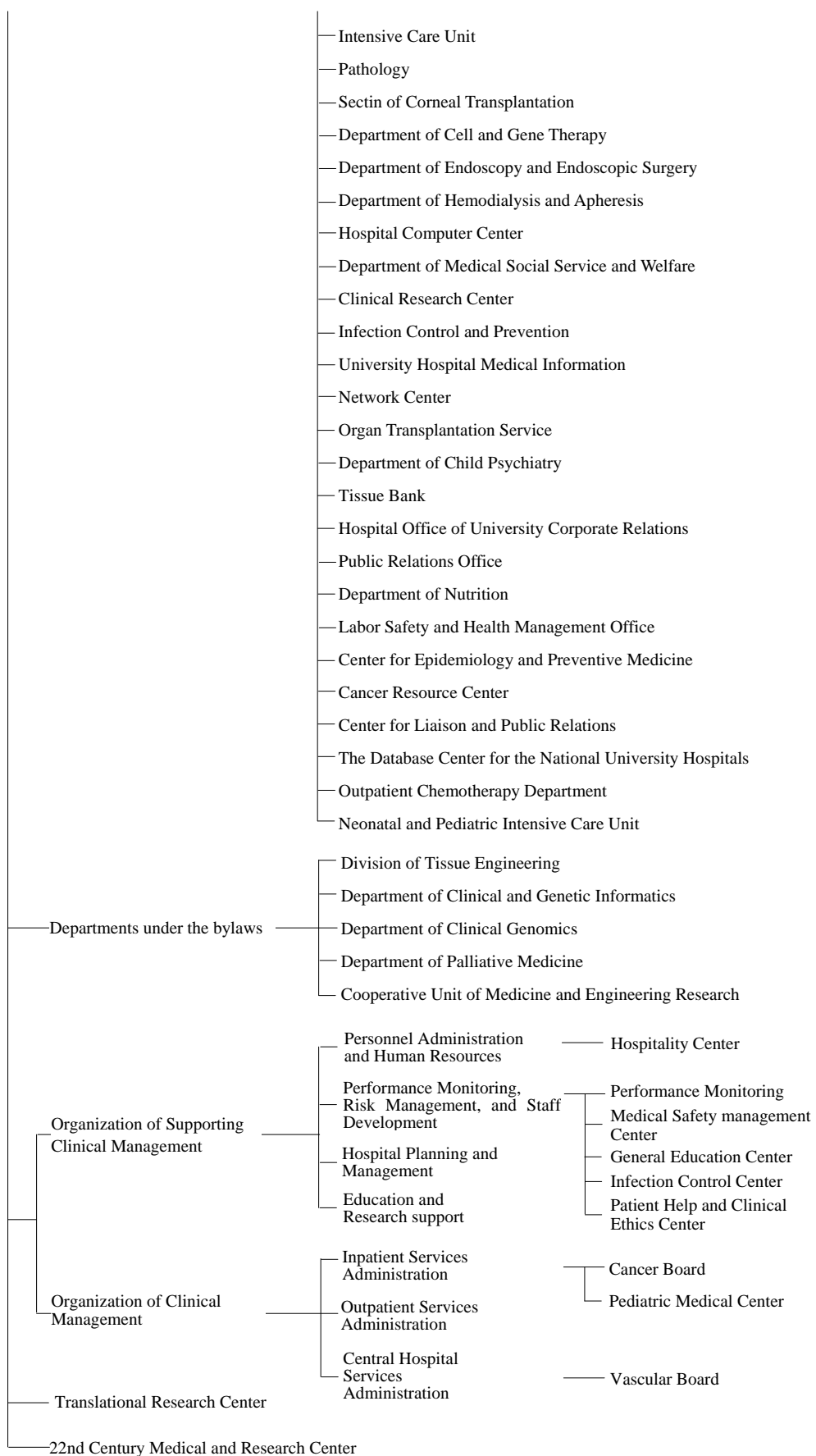












Teaching, Research, Secretarial and Administrative Staffs

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		Tadatsugu Taniguchi
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	Nobutaka Hirokawa
	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	Akio Nomoto
	professor	Kazuhiko Koike
Department of Immunology	professor	Tadatsugu Taniguchi

Radiology and Biomedical Engineering

Department of Radiology	professor	Kuni Otomo
Department of Biomedical Engineering	professor	Joji Ando

Neuroscience

Department of Basic Neuroscience	professor	Takeshi Iwatsubo
Department of Speech and Cognitive Sciences		

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	Masao Omata
Department of Medicine II	professor	Toshiro Fujita
	professor	Takashi Kadowaki
	professor	Mineo Kurokawa
	professor	Kazuhiko Yamamoto
	professor	Kazuhiko Koike
	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
Department of Pediatric Science	professor	Takashi Igarashi
	professor	Tadashi Iwanaka
Department of Aging Science	professor	Yasuyoshi Ouchi
Surgical Sciences		
Department of Surgery	professor	Shinichi Takamoto
	professor	Yasuyuki Seto
	professor	Norihiro Kokudo
	professor	Yukio honma
	professor	Hirokazu Nagawa
Department of Sensory and Motor System Medicine	professor	Kunihiko Tamaki
	professor	Isao Koshima
	professor	Tsuyoshi Takato
	Professor	Kozo Nakamura
	professor	Makoto Araie
	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	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	Atsuo Ogura
Laboratory of Molecular Radiology	professor	Kiyoshi Miyakawa
Division of Research Resources and Support		

International Academic Affairs

	professor	Kazuhiko Yamamoto
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Faculty of Medicine**Endowed Departments**

Department of Pharmacoepidemiology	Associate professor	Kiyoshi Kubota
Department of Integrated Traditional Medicine(Tsumura)		
	Associate professor	Tetsuro Okabe
Department of Corneal Tissue Regeneration (ArBlast Co.,Ltd.)		
	Associate professor	Satoru Yamagami
Department of Clinical Vascular Regeneration (Daiichi Pharmaceutical Co.)		
	Associate professor	Hiroyuki Koyama
Department of Bone & Cartilage Regenerative Medicine	professor	Yuichi Tei
Department of Cartilage of 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
Hospital Logistics by Sagawa Express Co.,Ltd.	professor	Hirohito Kuse
Clinical Molecular Epidemiology (Tanabe Seiyaku Co., Ltd.)	Associate professor	Takanari Gotoda
Immunotherapeutics (Medinet)	Associate professor	Kazuhiro Kakimi
Healthcare Related Informatics (NTT DATA CORPORATION)	Associate professor	Shinya Oku
Division of Total Renal Care Medicine	Associate professor	Akira Ishikawa
Integrated Molecular Science on Metabolic Diseases	Associate professor	Toshimasa Yamauchi
Department of Advanced Clinical Science and Therapeutics		
Sato Sports Plaza Co., Ltd Kaatsu Training	Associate professor	Toshiaki Nakajima
Translational Research Based on the Clinical Database	Associate professor	Hiroyuki Morita
Department of Joint Disease Research	Associate professor	Noriko Yoshimura
Health Care Management and Policy	Associate professor	Hideo Yasunaga
Computational Diagnostic Radiology and Preventive Medicine	Associate professor	Naoto Hayashi
	Associate professor	Kansei Uno
Hospital Environment	Associate professor	Yushi Uetera
Clinical Motor System Medicine	Associate professor	Toru Akune

Clinical Drug Evaluation	Associate professor	Fumihiko Kanai
Medical Safety Management (Tokio Marine & Nichido)	Professor	Yasushi Kodama
	Associate professor	Shoichi Maeda
Molecular Cardiovascular Metabolism	Associate professor	Katsuyuki Ando
The Department of Healthcare Quality Assessment	Associate professor	Noboru Motomura
Coca-Cola Anti-Aging Medicine	professor	Satoshi Inoue
Integrated Imaging Informatics	Associate professor	Naoki Yoshioka
The Department of Nutriproteomics	Associate professor	Kazumi Yagasaki
Clinical Epidemiology and Systems	professor	Tsutomu Yamazaki
	Associate professor	Daisuke Koide
Clinical Trial Data Management	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
Laboratory of Molecular Physiology on Energy Metabolism	Associate professor	Naoya Yahagi
Department of Molecular Neuroscience on Neurodegeneration	Associate professor	Atsushi Iwata
International Research Center for Medical Education	Director	Kazuhiko Yamamoto
	professor	Kiyoshi Kitamura
University Hospital		
Clinical Divisions		
General Medicine	Head	Kazuhiko Yamamoto
Cardiovascular Medicine	Head	Ryozo Nagai
Respiratory Medicine	Head	Takahide Nagase
Gastroenterology	Head	Masao Omata
Nephrology and Endocrinology	Head	Toshiro Fujita
Metabolic Diseases	Head	Takashi Kadowaki
Hematology and Oncology	Head	Mineo Kurokawa
Allergy and Rheumatology	Head	Kazuhiko Yamamoto
Infectious Diseases	Head	Kazuhiko Koike
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	Shinichi Takamoto
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	Kunihiko Tamaki
Ophthalmology and Vision Collection	Head	Makoto Araie
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
Transfusion Medicine and Immunohematology	Head	Koki Takahashi
Department of Maternal, Fetal, and Neonatal Medicine	Head	Takashi Igarashi
Rehabilitation Service	Head	Nobuhiko Haga
Department of Medical Engineering	Head	Hisayoshi Tamai
Central Supply Service	Head	Yoshikazu Mimura
Intensive Care Unit	Head	Naoki Yahagi
Intensive Pathology	Head	Masashi Fukayama
Corneal Transplantation	Head	Shiro Amano
Department of Cell Therapy and Transplantation Medicine	Head	Shigeru Chiba
Department of Endoscopy and Endoscopic Surgery	Head	Takao Kawabe
Center for Hemodialysis and Apheresis	Head	Toshiro Fujita

Department of Medical Social Service and Welfare	Head	Yasuyoshi Ouchi
Clinical Research Center(tentative name)	Head	Masao Omata
Infection Control and Prevention	Head	Kazuhiko Koike
Department of Planning, Information and Management	Head	Kazuhiko Ohe
University Hospital Medical Information Network Center	Head	Takahiro Kiuchi
Department of Organ Transplantation Service	Head	Norihiro Kokudo
Department of Child Psychiatry	Head	Takashi Igarashi
Tissue Bank	Head	Shinichi Takamoto
Center for Epidemiology and Preventive Medicine	Head	Tsutomu Yamazaki
Cancer Resource Center	Head	Shoichi Kaisaki
Center for Liaison and Public Relations	Head	Kazuhiko Ohe
The Database Center of the National University Hospitals	Head	Hiroshi Kushiya
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 Nalamura
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

Professor

Nobutaka Hirokawa, M.D.

Associate Professor

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Yasushi Okada, M. D., Yosuke Tanaka, M. D., Ryo Nitta, M. D.,
Noriko Homma, Ph. D., Harukata Miki, Ph. D., Hiroaki Yajima, Ph. D.
Tadayuki Ogawa, Ph. D.

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Teaching activities

Our teaching responsibility is following.

I.

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

II.

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

to medical students and students of other faculties.

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

Research activities

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

Our laboratory studies molecular architecture, dynamics and function of the neuronal cytoskeleton using various new molecular cell biological approaches including new electron microscopy such as the quick freeze deep etch electron microscopy, cryoelectron microscopy at atomic resolution, and cryoultramicrotomy, biochemistry, immunocytochemistry, molecular biology, molecular genetics such as gene targeting and transgenic mouse approaches, molecular biophysics and structure biology including X ray crystallography and cryoelectron microscopy.

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

Nerve cells as units of complicated neuronal networks in the brain develop very polarized morphology composed of dendrites, cell body and a long axon

along the direction of impulse propagation. The neuronal cytoskeleton plays three major important roles.

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

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

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

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Department of Cellular Neurobiology

Professor

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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 11 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.

The role of glia for synapse formation

Major structural components present in the vicinity of synapses are processes of glial cells. Electron microscopic analysis confirmed the presence of direct contacts between synapses and astroglial processes. By analyzing the relationship between astrocytic contacts and subsequent stabilization and maturation of spines, we found that local astrocytic contacts promote spine stabilization and structural maturation.

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Molecular Cell Biology

2. Biochemistry and Molecular Biology

Department of Molecular Biology

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Associate

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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. Molecular Mechanism for anchorage loss-induced Cdc6 degradation

In 2002, we reported that anchorage deprivation led to termination of expression of Cdc6, a factor essential for the assembly of Pre-RC, via Rb-independent transcriptional repression and papain family protease-led degradation. Subsequently, we identified the protease as lysosomal cathepsins, released from low cholesterol-content lysosomes upon anchorage deprivation. Although cathepsins appear to be the major Cdc6 degrading enzyme in NRK cells, they are not major ones in other cells such as mouse or rat embryonic fibroblasts. We recently found that two ubiquitin ligases are responsible for anchorage loss-induced Cdc6 degradation, one of which is identified as Cdh1-APC. One is likely to be FBW7 or a related. Another ubiquitin ligase is

likely to be responsible for degrading at least Cyclin A during anchorage deprivation and seemingly requires p53 for its activity. Its identity and the mechanism by which it requires p53 for its activity are unknown.

2. Identification of the signal pathways mediating signals for cellular anchorage to extra-cellular matrices

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 recently identified that the TSC1/2-Rheb-mTOR pathway appears to mediate an anchorage signal and controls at least the activity of Cdh1-APC an ubiquitin ligase that acts in G1 and degrades both Cdc6 and cyclin A. Active mTOR is required for inactivation of Rb together with activated cyclin D-dependent kinases. Inactivation of Rb activates E2F, resulting in induction of Emi1 as well as Cdc6 and Cyclin A. Induced Emi1 inactivates Cdh1-APC, thereby suppressing degradation of Cdc6 and Cyclin A. Search for the factor that links integrins and this pathway is underway and a candidate for it has already been found.

3. New function of Cdc6

Cdc6 is known as the assembler of pre-replicative complexes that is the initial step of chromosomal replication. We found that this factor has an additional function: the ability to activate p21^{WAF1}-inhibited Cdk2 in a ATP-dependent manner, the function never anticipated for Cdc6 and never anticipated for the regulation of a cyclin-dependent kinase. This unbelievable function of Cdc6 is confirmed by the essentiality of the "Cy" motif and the ATPase domain for this newly identified activity. Furthermore, we show that Cdc6 determines utilization of the p53-p21-dependent DNA damage checkpoint at least in S phase cells. Whenever Cdc6 is not destabilized, inactivation of Cdk2 by p21 is blocked in S phase. This discovery highlights the importance of Cdc6 as a focal point of the control of S phase onset and progression.

Our current studies indicate that Cdc6 might have two additional functions promoting S phase onset and progression.

p21^{WAF1/CIP1}-associated Cdk2 by Cdc6. 2008, Proc. Natl. Acad. Sci. USA. **105**, 4757-4762.

4. Induction of anchorage-independent proliferation of NRK cells by manipulation of four cell cycle and related factors

One approach to understand the mechanism of oncogenic transformation is to find a way to induce anchorage-independent proliferation of cells by manipulating cell cycle factors. This could be done with NRK cells and overexpression of three factors: Cdc6, Cdk6 and cyclin D3, the latter two of which can evade inhibition by inhibitor proteins and activate E2F under growth suppressive conditions like in anchorage loss-induced G1 arrest. Last year we succeeded in inducing anchorage-independent proliferation of mouse embryonic fibroblasts by overexpression of Cdk6, cyclin D3 and Cdc6. But the anchorage-independent proliferation was transient and lasted only one week. This year we have found the way to obtain continued anchorage-independent proliferation of embryonic fibroblasts. It can be achieved by additional expression of constitutively active mutant Rheb, which is a positive regulator of mTOR complex 1.

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.

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Department of Cellular Signaling

Professor

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Research Associate

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Introduction and Organization

In addition to the above 5 faculty members, we have 9 graduate students (9 doctor course students including 1 PhD-MD course students), and 4 undergraduate medical students (Free Quarter). Several clinical scientists and a research fellow from pharmaceutical company 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 2008 is over 17. For graduate course students, we have three-month lecture series (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 2000–5000 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 (JEOL HX 110, Hitachi M-80 and Finnigan MAT TSQ 7000 [ThermoQuest]) 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

In 2003, a new laboratory, Department of Metabolome was established by the donation of Shimadzu Co., Ltd, and Ono Pharmaceutical Co. Professor Ryo Taguchi and Associate Professor Yoshiya Oda are worldwide leading researchers on proteomics and metabolomics. 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, Nanobio Integration Program of the University of Tokyo, and a global COE program.

Publications

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Department of Physiological Chemistry and Metabolism

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Introduction and Organization

The Department of Physiological Chemistry and Nutrition, the predecessor of the present department, was founded in 1952. Upon the restructuring of the university system in 1997, the department was renamed 'Department of Physiological Chemistry and Metabolism' as one unit of the Specialty of Molecular Cell Biology. The present members include the above stuffs, 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/G₁₁-dependent signaling, while the formation of the distal pharyngeal region is under the control of a G_q/G₁₁-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 and epigenetics

To further understand the mechanisms of cell differentiation, we are studying how the DNA methylation status is controlled in preimplantation development and how reprogramming occurs after nuclear transfer. We identified the somatic type of DNA methyltransferase 1 as an enzyme responsible for maintenance methylation in preimplantation development.

(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

1. Physiology

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Introduction

This laboratory was initially established in 1877 as The First Department of Physiology, and reorganized in 1997 as Laboratory of Integrative Physiology in the Department of Physiology. Our laboratory cooperates with other laboratories in the Department of Physiology, that is, Laboratory of Molecular/Cellular Physiology and Laboratory of Neurophysiology, in teaching activities for undergraduate courses and the nursing school. The fields in which our laboratory specializes span the entire spectrum of *animal functions* of physiology, including general physiology, sensory physiology, endocrinology, neurophysiology, higher nervous functions and cognitive neurosciences.

Teaching activities

The staff members as well as experts from other universities (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 2 students (M3 and M4) continued to enjoy their researches from 2008 through 2009. 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, 4 postdoctoral researchers, 2 visiting scientist, 9 graduate students and 1 secretary staff.

Education

The department provides lectures and practice in physiology for undergraduate students. We teach electrophysiological methods and cell 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 mechanism for the perception of sensory inputs and for the emotional states induced by the sensory inputs. Our recent focus includes olfactory cortical mechanisms for recognizing food odors and for judging their edibility.

We have been investigating also the neuronal mechanisms for the incorporation of adult-born interneurons into the pre-existing neuronal circuit in the olfactory bulb, and the contact-mediated interactions between neurons and immune cells.

Currently we are focusing on the following three topics.

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

Based on the knowledge of the ‘odorant receptor maps’ in the olfactory bulb, we are studying the manner of olfactory information processing in the olfactory cortex and higher olfactory association regions. We found that individual neurons in the anterior piriform cortex integrate signals from distinct categories of food-born odorants. These

results suggest that the olfactory cortical neurons detect the odorant-category profile of foods in order to distinguish distinct food odors.

Individual neurons in the anterior olfactory nucleus also showed odorant category profile selectivity. Furthermore, for individual cortical neurons odorant category profile selectivity of left-nasal input was nearly equivalent with that of the right-nasal input.

We found also that neuronal circuit in the olfactory bulb can actively prolong the odor induced spike responses and thus keep the specific odor information for more than tens of seconds after the cessation of odor stimulus. In addition, we noted behavioral state-dependent change of the dendrodendritic synaptic inhibition in the olfactory bulb.

In addition, we found functional modularization in the odor maps of the olfactory bulb.

- (2) Cellular and molecular mechanisms for the contact-mediated interactions between neurons and immune cells in physiological and pathological conditions.

We are currently focusing on telencephalon-specific cell adhesion molecule, telencephalin. We are investigating the telencephalin-mediated signals between neurons and immune cells especially microglia during recovery from the neuronal damage.

- (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 the feeding-related time window of fate decision of newly-generated granule cells in the olfactory bulb, and current focus of our study includes the reorganization of the olfactory bulb circuit during and after the eating time.

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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. 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 endplate potential for understanding basic properties of synaptic transmission. Second, students record electromyogram (EMG) from human gastrocnemius muscles and learn how the stretch reflex works.

We accept Free-Quarter students. Students are encouraged to experience patch-clamp recordings from neurons either in brain slices or in dissociated culture, or to experience recordings of neuronal activities from living animals.

For the training of Master and Ph.D. course students, we have a weekly conference for discussing current research activities. A laboratory member summarizes his/her recent experimental data or presents papers closely related to his/her research. Moreover, for mutual communication between the laboratories with similar interests in neuroscience, we have a weekly joint seminar with Department of Cellular Neurobiology and Division of Structural Physiology.

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). For this purpose, we use various methodological approaches including electrophysiology, pharmacology, morphology, genetic engineering of mouse and optical imaging of functional molecules in living neurons. 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.

(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. 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 IP_3R indeed plays an essential role

in regulating the Ca^{2+} signal dynamics including Ca^{2+} oscillation.

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

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

2) Imaging of signalling molecules

Our study on Ca^{2+} signalling made us realize the importance of visualization of signalling molecules within living cells. Thus, our laboratory has been involved in the generation of new indicators of signalling molecules upstream and downstream Ca^{2+} signals. We have succeeded in imaging IP_3 signalling in various cells including intact neurons within cerebellar slice preparations. We also developed an indicator to detect the

phosphorylation of myosin regulatory light chain. The indicator allowed us to image phosphorylation state of myosin light chain in living cells. Furthermore, we generated a nitric oxide (NO) indicator based on the heme-binding domain of soluble guanylyl cyclase. This indicator was successfully used in cerebellar slice preparations to image NO signals in response to parallel fiber (PF) stimulation. We found that the NO signal intensity decreases steeply with distance 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 will provide the basis for the research of extrasynaptic glutamate transmission that is involved in many critical brain functions.

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

Although many important cell functions have been found to be regulated by Ca^{2+} signals, not all the Ca^{2+} -dependent cell functions have been identified. We are now searching for new cell functions that are regulated by Ca^{2+} signals.

Cells communicate with each other to form organized structures by cell-cell adhesion and cell-cell repulsion, but it remains to be clarified how cell-cell contact information is converted to intracellular signals. We found that cells in contact with neighbouring cells generate local transient intracellular Ca^{2+} signals (Ca^{2+} lightning). Ca^{2+} lightning was exclusively observed near cell-cell contact regions and was not observed in the central

regions of cells, nor was it found in solitary cells that are not in contact with other cells. We also show that Ca^{2+} lightning is capable of regulating cell-cell repulsion in a Ca^{2+} -dependent manner. These results demonstrated that cell-cell contact information may be transmitted by a new form of Ca^{2+} signal, Ca^{2+} lightning, to regulate intracellular events.

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

We have studied the role of IP_3 - Ca^{2+} signaling in astrocytes (the most abundant glial cells) and found that it regulates the expression of molecules on the surface of astrocytes that regulate the growth of neurons. Our results indicate that N-cadherin is involved in the regulation of neural growth. There seems to be more molecules that are involved in this mechanism, and we are searching for the new molecular mechanisms.

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 are now analyzing the basis of the cell-to-cell variability. It is expected that the study may provide 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 GluR1 by gene

targeting resulted in the increase of thresholds for both hippocampal LTP induction and contextual learning. Furthermore, cerebellar Purkinje cell (PC)-specific GluR δ 2 mutant mice showed impairment of cerebellar LTD and motor learning. These results suggest that GluR is a key molecule of learning and memory. 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. Interestingly, the NMDA receptor GluR ϵ 2 was essential for formation of the whisker-related neuronal barrelette structure in the brainstem trigeminal nucleus. The number of parallel fiber (PF)-PC synapses was decreased in GluR δ 2 mutant mice and multiple climbing fiber innervation was sustained. Thus, memory formation in the adult brain and synapse refinement during development may share common molecular mechanisms.

To investigate the molecular mechanism and regulation of learning and memory, we employed two approaches, conditional gene targeting on the pure C57BL/6 genetic background and neuron-specific gene manipulations in transparent zebrafish embryos. Brain functions are the products of dynamic interactions between multiple genes and environments. Accordingly, there are large differences among mouse strains at the behavioral and neurobiological levels.

Therefore, 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. We have established an inducible and neuron-specific gene targeting system on the pure C57BL/6 genetic background by employing Cre-progesterone receptor fusion recombinase for temporal regulation of gene targeting and Flp/frt recombination system for elimination of marker genes. Inducible ablation of GluR δ 2 in the adult cerebellum resulted in appearance of spines free from axon terminals and mismatching between active zone and PSD at PF-PC synapses. We thus identified GluR δ 2 as a key molecule that regulates pre- and postsynaptic matching and synaptic connection in the adult brain, providing evidence for the notion that there is a common molecular mechanism underlying synaptic plasticity and synapse formation. Among GluR δ 2-interacting molecules, we were interested in Delphilin because of its selective expression in cerebellar PCs. Ablation of Delphilin facilitated LTD induction at PF-PC synapses and enhanced 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 gain-increase adaptation, a simple form of motor learning. Studies on conditional mutant mice also revealed the involvement of striatal neurons in fear memory formation and the novel role of hippocampal NMDA receptors in network oscillation.

Transparent zebrafish embryos enable us to visualize synapse formation *in vi vo*. Using an olfactory sensory neuron-specific gene manipulation system with effector-reporter double-cassette vectors, we demonstrated that PKA-CREB signaling regulated synaptic vesicle accumulation in the axon terminals and calcineurin-NFAT signaling controlled morphological remodeling of the axon terminals during synapse formation. 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.

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Pathology, Immunology and Microbiology

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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”.

“Diagnostic Pathology” has been officially admitted in the fiscal year 2009 as the name of clinical department that can be shown to the patients. It was a great delight for us pathologists as indicating a general acceptance of the importance of pathology diagnosis.

Dr. Motoi moved to Teikyo University, School of Medicine as an Associate Professor. Drs. Sakatani and

Morikawa moved to the Division of Diagnostic Pathology, and Dr. Kikuchi was a new member of Associates. Dr. Takazawa and Dr. Shibahara were promoted to be Lecturer and Lecturer (Hospital), respectively. Dr. Yamauchi was employed by the global COE program, Chemical Biology of the Diseases, on September.

Two postgraduate students finished the course and received Ph.D. In the new fiscal year, 2009, four new students will enter the course, and there are 13 postgraduates (including one foreign student).

We are responsible for the pathology practice of The University Hospital, and carry forward the morphology-based research targeting human diseases. On the other hand, we take charge of General Pathology course for the 1st grade students in collaboration with Department of Molecular Pathology, and also Systemic Pathology, Clinical Clerkship, and Bedside-learning (BSL) for the 2nd–4th grade students.

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, brain, 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. They are useful for the education of clinical residents, in addition to the weekly autopsy conferences.

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 in corporation with Department of Legal Medicine. We have also started the two-year 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 2008 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 exercise is 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). All of the microscopes will be renewed and the virtual microscopy system will be introduced in the laboratory of the 2nd Building, partially by means of a financial aid from the head office of the university as one of its Education and Research Programs.

Clinical clerkship for the 3rd grade, and BSL for the 4th grade are carried out. In BSL, following courses are included; autopsy pathologic practices including a case presentation for paired students, surgical pathologic practices using various tumor sections, and a tour of the pathology laboratory.

The past examinations for the second grade students and for graduation are also referred to the website.

We have started the lecture series of tumor pathology for the Cancer Profession Training Program in postgraduate school, and the key slides are distributed as DVD to the students.

Research activities

The first major theme is “chronic inflammation and neoplasms”, for which various investigations are developed, in the fields of Epstein-Barr virus (EBV) associated gastric carcinoma (GC), lung carcinoma and scar formation, and carcinogenesis in pulmonary fibrosis. We clarified the role of latent membrane protein 2A in the development and progression of EBV-associated GC.

The second main theme is the 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. Drs. Ota and Shibahara carried out immunohistochemical studies with newly-developed monoclonal antibodies using the tissue microarray of various carcinomas.

Dr. Ishikawa developed a new method for analyzing the precise copy number of genes in genome wide (EG-method) in corporation with Prof. Aburatani (RCAST). It is the essential method for the medical research of the diseases, and he is expected to develop a new field of genome pathology. His method also gets a lot of attention from industries as a new method available for identifying the patients susceptible to adverse effects of a drug.

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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, a lecturer, two research associates, 4 technicians, and several research fellows, including 19 graduate students, 3 master course students, 2 post-doctoral fellows, and a guest research fellow from Sweden.

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. We have annual TGF- β meeting in Sweden every spring, and some graduate students participate in the meeting and orally present their results.

We are currently supported by the Global Center of Excellence (COE) Program for "Integrative Life Science Based on the Study of Biosignaling Mechanisms" from the Ministry of Education, Culture, Sports, Science and Technology of Japan. This program stimulates interaction with students and scientists in the program as well as those from other laboratories.

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.

Smad2 and Smad3 (Smad2/3) are primarily involved in the transmission of TGF-beta signaling from the cytoplasm to the nucleus. Many transcription factors have been reported to cooperate with Smad2/3 in regulation of the transcription of target genes. We have identified more than 1,700 Smad2/3 binding sites in the promoter regions of over 25,500 genes by chromatin immunoprecipitation on microarray (ChIP-chip) in human HaCaT keratinocyte cells. Binding elements for ETS1 and TFAP2A were enriched in the Smad2/3 binding sites, and knockdown of either ETS1 or TFAP2A resulted in alteration of TGF-beta-induced transcription. These findings suggest general roles of ETS1 and TFAP2A in the transcription induced by TGF-beta-Smad signaling pathways. We identified novel Smad binding sites in the CDKN1A gene where Smad2/3 binding was regulated by ETS1 and TFAP2A. Moreover, we showed that siRNAs for ETS1 and TFAP2A affected TGF-beta-induced growth arrest. We have also analyzed genes specifically regulated by Smad2 or Smad3, and found that their specificity was not solely dependent on the amounts of the Smad2 or Smad3 proteins bound to the promoters. These findings reveal novel regulatory mechanisms of Smad2/3-induced transcription in TGF-beta signaling pathways (Koinuma et al., *Mol. Cell. Biol.* 2009).

Epithelial-to-mesenchymal transition (EMT) is a crucial event for cancer cells to acquire invasive and metastatic properties and is induced by TGF-beta. We found the mechanism whereby Snail, a key transcriptional regulator of EMT, is induced by TGF-beta in cancer cells. Snail induction by TGF-beta was highly dependent on cooperation with active Ras signals, and knockdown of Ras abolished induction of Snail by TGF-beta in a pancreatic cancer cell line Panc-1. Exogenous expression of active Ras into

HeLa cells resulted in induction of Snail by TGF-beta, while expression of other target genes of TGF-beta, e.g. Smad7 and PAI-1, was not affected by Ras signaling. We found that phosphorylation at the linker region of Smad2 or Smad3 by MAP kinases was not essential for the induction of Snail by TGF-beta. Our findings indicate that Ras and TGF-beta signaling cooperate in the induction of Snail, which occurs in a Smad-dependent manner (Horiguchi et al., *J. Biol. Chem.* 2009).

Thyroid transcription factor-1 (TTF-1, also known as Nkx2.1) is expressed in lung cancer, but its biological functions are unknown. We have found a novel function of TTF-1 that inhibits TGF-beta-induced EMT and restores epithelial phenotype in several lung adenocarcinoma cells. The effect of TTF-1 was accompanied by down-regulation of some TGF-beta target genes, including above-mentioned EMT regulators, such as Snail and Slug. Silencing of TTF-1 enhanced TGF-beta-induced EMT, and thus, TTF-1 exerts a tumor-suppressive effect with abrogation of cellular response to TGF-beta. Moreover, we have found that TTF-1 reduces TGF-beta2 production in lung adenocarcinoma A549 cells and that TGF-beta conversely decreases TTF-1 expression. These findings suggest that enhancement of autocrine TGF-beta signaling facilitates the decrease of TTF-1 expression and vice versa, and that regulation of TTF-1 expression can be a novel therapeutic strategy for treatment of lung adenocarcinoma (Saito et al., *Cancer Res.* 2009).

We previously reported the use of TGF-beta inhibitor on tumor neovasculature in stroma-rich tumor models (such as pancreatic cancer models) to increase the intra-tumoral distribution of nanoparticles. We compared the effects of two other protein kinase inhibitors, imatinib and sorafenib, with TGF-beta inhibitor (LY364947) on extravasation of a modelled nanoparticle, i.e. 2 MDa dextran. We first used a Matrigel plug assay to compare neovasculature formed inside of and around Matrigel plugs (intra-plug and peri-plug regions, respectively). Intra-plug neovasculature was more abundantly covered by pericytes, while peri-plug neovasculature was less covered. TGF-beta inhibitor showed the most potent effect on intra-plug neovasculature in increasing the extravasation of dextran, while

sorafenib showed the most potent effect on peri-plug neovasculature. Next, these findings were confirmed by using two tumor models, i.e. the CT26 colon cancer and the BxPC3 pancreatic cancer models. The neovasculature phenotype in CT26 was similar to that in the peri-plug region, while that in BxPC3 was similar to that in the intra-plug region. Consistently, sorafenib potently enhanced the accumulation of nanoparticles in the CT26 tumors, while TGF-beta inhibitor did so in the BxPC3 tumors. Thus, the strategy for optimization of tumor neovasculature for nanoparticles may be different, depending on tumor types (Kano et al., *Cancer Sci.* 2009).

During the process of embryonic lymphatic development, a homeobox transcription factor, Prox1, is expressed in a subset of venous blood endothelial cells (BECs) in which an orphan nuclear receptor, COUP-TFII, is highly expressed. Prox1 induces differentiation of BECs into lymphatic endothelial cells (LECs) by inducing the expression of various molecules responsible for LEC differentiation, including vascular endothelial growth factor receptor 3 (VEGFR3). However, mechanisms how transcriptional activities of Prox1 are regulated remain to be studied. We have found that Prox1 induces the proliferation and migration of BECs and LECs toward VEGF-C by inducing the expression of cyclin E1 and VEGFR3, respectively. Gain-of-function studies showed that COUP-TFII negatively regulates the effects of Prox1 in BECs and LECs. We also showed that Prox1 and COUP-TFII physically interact with each other in LECs and that they both bind to the cyclin E1 promoter. These findings suggest that COUP-TFII physically and functionally interact during differentiation and maintenance of lymphatic vessels (Yamazaki et al., *Gene Cells*, 2009).

We have organized Sapporo Cancer Seminar "TGF-beta signaling and cancer" on June 26-27, 2009 in Sapporo (supported by the Global COE Program). More than 150 scientists and students participated in the Seminar, and exchanged their most recent data.

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Pathology, Immunology and Microbiology

2. Microbiology

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Introduction and Organization

Microbial disease has been recognized as the major threat to human health throughout the history. Despite the development of preventive and therapeutic interventions against some pathogenic microbes, infectious disease is still one of the most significant medical problems. On the other hand, microbial organisms have served as a useful model as well for elucidating the molecular mechanisms of a variety of biological events, providing useful insights into life science. Recently, efforts have also been initiated by a number of research groups to utilize animal viruses as a tool for human gene therapy. In order to familiarize students with these issues, importance of microbiology in medical education is increasing more rapidly than ever. To fulfill this requirement, our department, as the only basic microbiology unit in the Faculty, currently assumes a responsibility for teaching bacteriology, mycology, and virology to medical undergraduates.

Education

Undergraduate Course, Faculty of Medicine

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

In addition to the staff of our department, experts from the National Institute of Infectious Diseases (Dr. Watanabe and Dr. Yoshikura), Faculty of Agriculture (Dr. Onodera), Institute of Medical Science (Dr. Sasakawa, Dr. Kawaoka, Dr. Iwamoto, Dr. Saito, and Dr. Matano), and professor emeritus (Dr. Kawana) contribute to the teaching activities.

Research

1. **IRES (internal ribosome entry site)-dependent translation**
Kamoshita, N., Munakata, T., and Nomoto, A.
2. **PVR (poliovirus receptor)-dependent and -independent poliovirus entry**
Ohka, S., Nihei, C., Mikame, M., and Nomoto, A.
3. **Effect of viral infection on cell metabolism**
Kamoshita, N., Matsuda, N., Nihei, C., Ohka, S., and Nomoto, A.
4. **Blood brain barrier permeation of poliovirus**
Mikame, M., Nihei, C., Ohka, S., and Nomoto, A.
5. **Oral infection mechanism of poliovirus**
Ohka, S., Kajiro, K., and Nomoto, A.
6. **Development and application of poliovirus vector**
Chiba, H., Igarashi, H., Shimizu, M., Ohka, S., and Nomoto, A.
7. **Biochemical analysis of HCV (hepatitis C virus) genome as an RNA replicon**
Okamoto, Y., Munakata, T., Kamoshita, N., and Nomoto, A.

8. Molecular basis for HCV pathogenesis

Munakata, T., Hayase, N., and Nomoto, A.

9. Development of novel inhibitors of HCV replication

Munakata, T., and Nomoto, A.

Publications

1. Nishimura T, Saito M, Takano T, Nomoto A, Kohara M, and Tsukiyama-Kohara K. Comparative aspects on the role of polypyrimidine tract-binding protein in internal initiation of hepatitis C virus and poliovirus RNAs. *Comparat Immunol Microbiol Infect Dis.*, 31: 435-448, 2008.

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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, two lecturers, 6 guest lecturers, two 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 au reus* 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 3rd and 4th grade students and lectures on infectious diseases for the 4th grade students), the course of health science (lectures on microbiology), and the school of nursing (lectures and practical exercises on microbiology). 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:

- 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 microorganism infection
- 9) New detection method and pathogenesis of opportunistic cytomegaloviral infection
- 10) Mechanism of multi-drug resistant microorganisms

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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 Dr. Tomio Tada, now Professor Emeritus of The University of Tokyo, 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, Dr. Taniguchi had tried to follow and improve the high standards of the department established by Dr. Tada 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, Prof. Taniguchi's research was the first to identify and subsequent 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 encompass a number of areas including those

pertaining to innate immune system activation, autoimmunity, oncogenesis, and others.

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 question 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).

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. We further identified several important domains of DAI, and revealed that DAI forms a multimer upon DNA recognition to activate the down-stream signaling pathways. We have established DAI-deficient mice and plan to investigate the physiological role of DAI.

With respect to IRF-mediated regulation of apoptosis, we have shown that IRF-5, previously shown by us to be important cytokine gene induction, also regulates cellular susceptibility to apoptosis triggered by various stimuli such as virus, DNA damage, and death receptor Fas. In addition, we have demonstrated that IRF-5 has tumor suppressive activity. Therefore, IRF-5 is important for two main

aspects of immune homeostasis and host defense, namely in generating immune responses to invading pathogens and suppression of tumor development. Another recent, critical finding is that IRF-1 transactivates the IL-12 receptor β gene, thereby supporting Th1 differentiation. These are just a small subset of the scientific questions related to the IRF family of transcription factors, which serves to illustrate the important role they serve in host defense system. Future studies by our and other labs will continue to reveal their functions.

In addition to their roles during pathogen challenge, type I IFNs are known to be produced at low levels in the absence of infection. Recently, we demonstrate that a weak signal by these constitutively produced type I IFNs plays a preventive role in cellular transformation. IFN receptor AR1 (IFNAR1)-deficient (*Ifnar1*^{-/-}) MEF, which are unable to receive signals by type I IFNs, undergo spontaneous cellular transformation during long-term cell culture without any abnormal growth properties. Furthermore, *Ifnar1*^{-/-} mice develop chemically induced skin papilloma more severely than wild-type mice and the expression of IFNAR1 mRNA are significantly decreased in human gastric cancer tissues. Collectively, these findings suggest a cell-intrinsic role of the weak signal by constitutively produced type I IFN to prevent cells from transformation.

In addition to advancing a basic understanding of the principles of immunology, we are also trying to establish therapeutic strategies for the treatment of cancer. The selective elimination of tumor cells is one of the most important issues in cancer therapy. In this context, we recently revealed that Noxa, a BH3-only protein with proapoptotic activity, selectively induces apoptosis in human tumor cells. Upon infection of a recombinant adenovirus contrived to express the *Noxa* gene, apoptosis was induced in several human breast cancer cell lines, but not in normal mammary epithelial cells. Furthermore, intratumoral injection of the Noxa-expressing adenovirus resulted in marked shrinkage of the transplanted tumor without any notable adverse effect on the surrounding normal tissue. These data provide a new prospect for cancer therapy by the Noxa-mediated selective elimination of malignant cells.

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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 was kicked off recently.

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 ra-

dionuclide (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, sixteen 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 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. Application of an open-type MR imaging unit to interventional radiology is another field of clinical research. In our section, MR imaging is specifically used to the treatment of vascular malformation. Basic animal experiments are also in progress in the field of functional MR imaging and diffusion and perfusion MR techniques.

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

Our department originated from the Institute of Medical Electronics, established in 1961. In 1997, as a result of the shift to the chair system of the Graduate School of Medicine, the Institute was replaced with three departments of Biomedical Engineering: System Physiology, Bioimaging and Biomagnetics, and Biosystem Construction and Control. The Department of System Physiology consists of one professor and one lecturer.

Teaching activities

We provide lectures of “Early Exposure to Medicine” for first year students, “Basic Principles of Biomedical Engineering” for second and third year students, “Introduction to Biomedical Engineering” for postgraduate students, “Introduction to Medical Science: Medical Engineering” for master’s students, in the faculty of Medicine, and “Principles of Medicine” for postgraduate students in the faculty of Engineering. We offer practical training of biomedical engineering research to third and fourth year medical students. A weekly seminar is held in our laboratory bringing together staff, postgraduate students and research fellows to discuss journal articles and give updates on experiments. Our aim is to enhance the research skills of students.

Research activities

This laboratory has been pursuing the study of

biomechanics dealing with mechanical phenomena in the human body, especially focusing on cellular sensing and response mechanisms to mechanical stimuli. The main theme of our work is the relationships between shear stress, a mechanical force generated by blood flow, and its target cells, vascular endothelial cells. This would be of benefit not only to understanding blood flow-mediated regulation of vascular functions but also to the elucidation of clinically important problems such as angiogenesis, vascular remodeling and atherogenesis which occur in a blood flow-dependent manner.

Original biomedical engineering methods have been applied, in which cultured endothelial cells are exposed to controlled levels of shear stress in a fluid-dynamic flow apparatus and whose responses are analyzed at the cellular and molecular levels. Microcirculatory hemodynamics and oxygen transport are studied by employing opto-electronics technology. The results of these experiments are listed below.

1. Cell responses to shear stress
2. Shear stress-mediated gene regulation
3. Shear stress signal transduction

1. Cell responses to shear stress

Our studies have demonstrated that endothelial cells have functional responses to shear stress. When a cultured endothelial cell monolayer was partially denuded, surrounding cells migrated and proliferated in the denuded area, and covered the denuded area. Shear stress enhanced the regenerative functions of endothelial cells (Microvasc Res 1987, Biorheology,

1990). Shear stress increased the production of nitric oxide, a potent vasodilator, in endothelial cells in a dose-dependent manner (BBRC 1994). Shear stress also increased the expression of thrombomodulin, an antithrombotic molecule, in endothelial cells (BBRC 1994). In contrast, it decreased the expression of vascular cell adhesion, which leads to the inhibition of leukocyte adhesion to vascular cell adhesion molecule-1 (VCAM-1; BBRC 1993, Am J Physiol 1994). A collaborative study showed that shear stress increases the levels of adrenomedullin and C-type natriuretic peptide mRNA which have vasodilating effects in addition to nitric oxide (Hypertension 1997), and that it also augmented the expression of lectin like low density lipoprotein receptor (LOX-1) at the protein and mRNA level (Circ Res 1998). Recently, we revealed that endothelial progenitor cells (EPCs) circulating in human peripheral blood proliferate and differentiate into mature endothelial cells in response to shear stress, thereby forming tube-like structures in collagen gel (J Appl Physiol 2003). We also found that shear stress induces the differentiation of murine embryonic stem cells (ES cells) into endothelial cells in vitro (Am J Physiol 2005). Based on these findings, in a collaborative study, a new type of artificial blood vessel, in which ES cells were cultured in polymer tubes and exposed to pulsatile shear stress, was developed (J Artif Organs 2005). More recently, we revealed that shear stress increased the gene expression of the arterial EC marker ephrinB2 in EPCs, while it decreased the gene expression of the venous EC marker EphB4, suggesting that shear stress affects arterial-venous differentiation of EPCs (J Appl Physiol 2009).

2. Shear stress-mediated gene regulation

We have demonstrated that shear stress regulates endothelial gene expression transcriptionally and/or posttranscriptionally. Shear stress downregulates VCAM-1 gene transcription via the double AP-1 binding element (TGAACA) in the promoter which functions as a shear stress-responsive element (Am J Physiol 1997). Shear stress has also been shown to increase the level of granulocyte/macrophage-colony stimulating factor (GM-CSF) via mRNA stabilization

(Circ Res 1988). Differential display analysis showed that around 600 known and unknown transcripts were up- or down-regulated in human umbilical vein endothelial cells exposed to a shear stress of 15 dynes/cm² for 6 h (BBRC 1996). From these shear stress-responsive genes, a cDNA encoding an unknown G-protein coupled receptor was cloned (BBRC 1997). We showed that the transcription factor SP1 is involved in the shear stress-induced down-regulation of P2X4 (an ATP-gated cation channel) gene expression in endothelial cells (Am J Physiol 2001). DNA microarray analysis revealed that approximately 3% of the all endothelial genes, which corresponds to about 600 genes, respond to shear stress (J Athero Thromb 2003). Recently, we revealed that endothelial genes are differentially regulated by laminar and turbulent shear stress. Laminar shear stress decreases the gene expression of urokinase plasminogen activator (uPA), which plays a role in fibrinolysis and vascular remodeling, via both GATA6-mediated down-regulation of gene transcription and an acceleration of mRNA degradation, while turbulent shear stress increases the uPA gene expression through mRNA stabilization (Am J Physiol 2004). We demonstrated that shear stress up-regulates the gene expression of plasminogen activator inhibitor-1 (PAI-1) through activation of transcription factors Sp-1 and Ets-1 in human hepatocytes (Am J Physiol 2006). We developed a compliant tube-type flow-loading device that allows simultaneous application of physiological levels of shear stress and cyclic strain to cultured cells and observed that the response of endothelial genes to shear stress or cyclic strain depends on whether the two forces are applied separately or together (J Biotechnology 2008).

3. Shear stress signal transduction

We first showed that Ca²⁺ signaling plays an important role in the mechanism by which endothelial cells recognize the shear stress signal and transmit it into the cell interior (In Vitro Cell Dev Biol 1988). Strong shearing forces induced by dragging endothelial cells with a balloon causes an increase in cytoplasmic Ca²⁺ concentrations (Biorheology 1994). A relatively weak shearing force like shear stress

generated by fluid flow needs the presence of extracellular ATP to induce Ca^{2+} response, and at several hundred nanomolar of ATP, intracellular Ca^{2+} concentrations increase in a shear stress-dependent manner (BBRC 1991, 1993). Generally, flow-induced Ca^{2+} responses are initiated at a locus at the cell edge and propagate throughout the entire cell in the form of a Ca^{2+} wave. The initiation locus corresponded precisely to caveolae rich cell edges (Proc Nat'l Acad Sci 1998). We found that a subtype of ATP-gated cation channel, the P2X4 receptor, is expressed in human vascular endothelial cells (Am J Physiol 2000) and that P2X4 receptors play a crucial role in the shear stress-dependent Ca^{2+} response (Circ Res 2000). Endogeneously released ATP by shear stress is involved in the P2X4-mediated Ca^{2+} responses (Am J Physiol 2003). We produced *P2X4*-deficient mice and observed that the *P2X4*-deficient mice have impaired flow-dependent control of vascular tone and remodeling, indicating that shear stress signal transduction via P2X4 plays a critical role in the regulation of circulatory functions (Nat Med 2006). Our recent study revealed that cell surface ATP synthase localized in caveolae/lipid rafts are involved in the shear-stress-induced ATP release by ECs (Am J Physiol 2007).

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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 of the therapeutic medical engineering technologies in 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 the clinical medicine. The name of the department and institute has been changed as shown above since April 1, 1997 with the structural reformation of the Faculty of Medicine.

The research covers wide area of interdisciplinary and comprehensive research fields based on the medical and engineering techniques, we are cooperating with various laboratories. Our doctor course students have the opportunity to perform research work under the guidance of Prof. Mabuchi at Department of Information Physics and Computing, Graduate School of Information Science and Technology.

Teaching activities

As for under-graduate education, our department takes a part in systematic lectures for the 3rd year medical students, and provides practice in the “free quarter” course for the 3rd and 4th year medical students. In systematic lectures, basic knowledge for the advanced diagnostic and therapeutic medical engineering

technologies are presented. The basic lectures of artificial organ technologies are included.

As for post-graduate education, our department takes a part in series of lectures for master course and doctor course students. In the lectures for master course students, artificial organ technologies are presented. In the lectures for doctor course students, philosophy, methodology and basic and special knowledge about medical engineering high technologies for basic and clinical medicine are presented.

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 much other important information are acquired through the fabrication and the animal experiment of artificial hearts. As for the subject of research, students find by themselves not only from the field of artificial organs but also from the wide area of medical engineering fields. On the other hand, the education to train the leaders of biomedical engineers and clinical engineers is another important role. Students must attend to weekly meeting. They can learn how to perform the research work and how to report it through this meeting.

Research activities

Our research field covers advanced diagnostic and therapeutic medical engineering high technologies for

clinical medicine. The main themes are artificial organs (artificial heart, assist circulation, artificial lung, artificial valve, tissue engineered artificial organs, regenerative artificial organs, etc). Especially, artificial heart is the world famous research project having a long history since 1959 at the University of Tokyo. 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 participating in the artificial heart project. In 1995, we succeeded to survive a goat for 532 days with the paracorporeal total artificial heart (TAH), which is still the longest survival 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, to meet the purpose. 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 pulsatile flow by changing motor speed periodically. Recently, the new model of UPTAH was developed for the purpose of studying physiology with nonpulsatile TAH. This UPTAH can switch pulsatile flow to nonpulsatile flow with a single device easily. We succeeded to survive a goat for 153 days with UPTAH.

How to control the output of TAH is another big interest. We have developed our original control method, named 1/R control, in which the cardiac output is controlled by the cardiovascular center through the feedback mechanism using changes in total peripheral resistance and arterial pressure. At the present time, 1/R control is the only reported method to achieve a physiological control of a TAH logically. With 1/R control, the particular problems of 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 condition of the animal.

1/R control was installed in the UPTAH and the

pathphysiological study was performed with nonpulsatile TAH. The result showed that 1/R control could be possible not only with a pulsatile TAH, but also with a nonpulsatile TAH. The general condition and organ function were not changed by the application of the nonpulsatile mode. Cardiac output and arterial pressure changed with the condition of the goat in pulsatile and also in nonpulsatile modes, which seemed almost identical. However, the sucking effect of atria was very significant in the nonpulsatile mode, resulted in hemolysis. Therefore, nonpulsatile TAH with 1/R control was considered to be inadequate, unless some pulsatility would be introduced to avoid fatal sucking effect for ensuring sufficient inflow condition.

A project of ELSS (Emergency Life Support System) that is a compact PCPS (Percutaneous cardio pulmonary support) device for emergency use has been started in 2004. The device consists of blood pump, oxygenator, drive and control unit and battery unit. A new membrane oxygenator and a new blood pump were designed and fabricated in one piece. An experimental model exhibited good performance. The whole system components are packed in a case having 180 mm in diameter and 390 mm long. The whole weight will be less than 10 Kg.

Concerning the biomaterials, the mechanisms of thrombus formation and calcification on the medical polymer surfaces have been studied. Recently, we developed the new hybrid technique. In general, it was not easy to develop the mechanical components of implantable artificial organs from the components of living tissue because strength and durability are not enough. To overcome the problem, a tissue engineered insert molding method for making parts of artificial organs was introduced. In the method, the mold in which the artificial material is inserted was implanted in the animal, and the tissue grew into the mold to make the hybrid parts. The method was applied to the Jellyfish valve. The hybrid Jellyfish valve demonstrated a possibility of the method for practical use. This hybrid biomaterial technique will be important technology for developing next generation artificial organs.

An implantable probe for observation of microcirculation has been developed using CCD chip. This device is expected to progress the physiology of

the microcirculation with TAH. This device has made a remarkable progress to make a next generation device. The new implantable probe can observe angiogenesis in tissue-engineered material using CMOS camera. In this method a scaffold was attached to the camera and implanted in the animal. The camera succeeded to observe the real-time growth of tissue and micro vessels in the scaffold. This technique will give important information for the studies of tissue engineering and regenerative medicine as well as implantable artificial organs.

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.

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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 drug, 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 cysteine 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 post-mortem 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, two assistant professors, two postdoctoral scholars,

one technical staff member, two Ph.D. and two 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 21st Century Center of Excellence Program Grant "Center for Integrated Brain Medical Science". 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. 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). This hypothesis is now being tested.

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; Fuse et al. in press), we identified a novel CaMKI isoform that contained a C-terminal CAAX lipid modification motif (Takemoto-Kimura et al., J. Biol. Chem., 2003). 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, Ageta-Ishihara et al., Neuron, 2007).

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 mDial1 to actively mediate its effect on actin nucleation and polymerization (Arakawa et al., J. Cell Biol., 2003; Yamana et al., Mol. Cell Biol. 2006).

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 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.

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. we concluded that improved EPRIL method was applicable to production of genome-wide RNAi library.

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Neuroscience

2. Speech and Cognitive Sciences

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Homepage

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. How? Let's discuss.

- 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 beha-

vioral 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 and 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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Neuroscience

3. Clinical Neuroscience

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Introduction and Organization

The Department of Neuropsychiatry is Japan's oldest psychiatric department which was established in 1886. "Anti-Psychiatry" movement for the last 3 decades had highly negative effects on the progress in all aspects of our activities. However, since 1994, our department has been normalized and restarted to play a leading role in psychiatry in Japan. Now the Department of Neuropsychiatry provides a wide-ranged clinical, training, and research services. Since August 2006, we have been working in the new closed ward (30 beds) and in the open ward (30 beds). Moreover, since 2000, we have been supported by a government grant for basic and clinical neuroscience in stress-related disorders including posttraumatic stress disorder (PTSD). Since 2005, we have begun to focus on basic and clinical neuroscience in pervasive developmental disorders (PDDs).

Clinical activities

For outpatient services, we have more than 20 staff psychiatrists, 4 clinical psychologists, 2 trained nurses, and 1 psychiatric social worker. Approximately 1100 new patients visited yearly (2007), and the total visits per year was about 43,000 (140 per day).

The secluded ward has 29 beds including 3 seclusion rooms. We also have 31 beds for the open general ward. Approximately 470 patients with various psychiatric disorders were admitted in a year (2007), about one-third of whom were referred from the emergency unit. Occupational therapy, recreational therapy, group therapy, and art therapy are performed.

We established Japan's first child psychiatry day care unit in national university hospitals in 1967. As children with Down's syndrome began to be accepted into nurseries and kindergartens around the year 1975, the focus of this division shifted to the psychological pedagogy of autism. Treatment of autism changed along with the understanding of the clinical condition,

from behavioral therapy to cognitive development based therapy. Since 1997, our division was reduced in size and an improved therapy system, “developmental psychology outpatient clinic” was established. This outpatient clinic encompasses individual treatment and psychological counseling by clinical psychologists under the supervision of psychiatrists. Our staff includes 1 full-time psychiatrists, 4 part-time psychiatrists, and 3 clinical psychologists. We provide care for 260 autistic or developmentally disabled children per year. Since 2000, a short term therapy group program has started. Parents participated in the treatment program alongside the staff members. This not only emphasizes the therapy of the child, but assesses their developmental level from many directions. The purpose of the therapy program is to help parents gain a better understanding of children’s disability and to help them to acquire a more supportive role for their children in the home environment. Since 2005, we have established clinical and educational center for developmental disorders, and provided clinical and educational activities in pervasive developmental disorders.

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.

Research activities

Stress- It is well accepted that neuropeptide Y (NPY) is involved in anxiolytic-like effects and anti-stress effects. Pharmacological and behavioral studies have consistently indicated that these effects are mainly mediated through an activation of NPY Y1 receptor in the brain. To further elucidate the functional role of Y1 receptor, we have evaluated the

histological and behavioral changes in Y1 receptor-deficient mice, after an exposure to 2h of restraint stress. Trimethyltin (TMT), a neurotoxic organotin, has been shown to cause selective loss of pyramidal neurons in the rat hippocampus, similar to stress-induced hippocampal changes. Several recent studies in animal models of brain ischemia revealed the neuroprotective properties of tacrolimus (FK506), a potent immunosuppressant used in organ transplants. Therefore, we have investigated the effect of FK-506 on the neuronal death and apoptosis in the hippocampus after TMT intoxication, using immunohistochemistry and TUNEL method.

Epilepsy- Systemic injection of kainic acid in rat causes severe convulsions, increased seizure susceptibility and seizure-induced neuronal death. Since precise mechanisms of various anticonvulsants are still unclear, we have investigated to elucidate whether these anticonvulsants demonstrate neuroprotective effects on kainic acid-induced neuronal death in the hippocampus.

Environmental endocrine disrupter- Bisphenol-A (BPA), one of environmental endocrine disrupters, is released from polycarbonate plastics, and is known to mimic oestrogens in their action. Recent studies reported that prenatal and neonatal exposure to low-dose bisphenol-A modulates the sexual differentiation of behavior and the central dopaminergic effects in vivo and in vitro. We examine the effects of BPA on the behavior, memory and the expression of estrogen-alpha receptor in the brain of rats exposed to BPA during the fetal and suckling periods at a dosage far less than the no-observed-adverse-effect level.

Genetic 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, infantile 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. We are at present achieving most interesting results in the investigations of DISC1, Neuregulin1 and other candidate genes in schizophrenia and the chromosome 7 genes in

infantile autism. Another focus is investigation of genes that affect the development of personality.

Neuroimaging- Our group plays a leading role in psychiatric neuroimaging in Japan. Our research 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).

Clinical Pharmacology- The atypical neuroleptics have been widely prescribed in our country. They contribute to the reduction of uncomfortable side effects and the improvement of the patient's QOL. But the typical neuroleptics still have been used because of their sedative effects particularly in acute state of Schizophrenia. We have been investigating a voluntary clinical research, which contain the practical evaluation to the treatment of atypical neuroleptics for acute psychotic state in Schizophrenia.

Recently the abnormal glucose tolerance induced by atypical neuroleptics had been reported and some accidental hyperglycemia had happened in our country, too. Though there are many reports involving to this problem in foreign country, few detailed investigation was performed in Japan until now. We are preparing to examine the glucose tolerance of inpatients that are treated by neuroleptics in collaboration with many hospitals and expect that the frequency of risk and some actual factors will be revealed.

Neuropathological study of dementias- Our interest is neuropathological background of dementia, especially NFT-predominant form of dementia (NFTD). NFTD is a sporadic subset of dementia pathologically characterized by abundant and almost exclusive appearance of NFTs in the limbic areas with scarcity of senile plaques. Our study suggests that pathogenetic background of NFTD may be different from that of AD and cognitive decline in NFT-SC may be affected not only by severity of NFT pathology but also by coexisting vascular lesions and/or argyrophilic grains.

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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. 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., Deoka, K., Ishiura, H., Ihara, R., Hahimoto, A)

We have demonstrated that RNA editing of glutamate receptor subunit GluR2 due to underactivity of ADAR2, an RNA editing enzyme, was significantly reduced in motor neurons in sporadic ALS patients in a neuronal class-selective and disease specific manner. Since this molecular change is the primary causes of neuronal death, research work on elucidation of the underlying molecular mechanism and development of specific therapy for sporadic ALS is undergoing. (Kwak, S., Hideyama, T., Yamashita, T., Awabayashi, K., Ymada Y.)

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 ECG. 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., Terada, S., Yugeta, A., Hamada, M., Matsumoto, H., Furubayashi, T., Higashihara, M., Shirota, Y, Ohminami, S.)

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., Mashiko, R.).

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Introduction and Organization

The Department of Neurosurgery at the University of Tokyo Hospital consists of 14 staff neurosurgeons, who participate in the three major academic activities: patient care, research and education. The staffs include a professor/chairman, two associate professors, three lecturers and nine 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.

Clinical activities

General and specialized outpatient clinics are open 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, epilepsy, and gamma knife treatment. From April 2008 through March 2009, 14,447 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 2007 and 2008, 482 and 731 patients were admitted to the Neurosurgical Ward, respectively. Four hundred and four and 367 surgical procedures were performed with 147 and 135 gamma knife procedures 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.

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 42 neurosurgical institutions in and around the city of Tokyo including 15 university medical centers, where our residents and students are exposed to various pathologies. Surgical case volume in all hospitals exceeds 5500 cases.

Teaching activities

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

We accepted 6 residents in 2008 as a new 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 currently prepare a clinical trial on patients with progressive glioblastoma. Using our HSV vector construction system, we further create and test various oncolytic HSV vectors "armed" with immunostimulatory genes. We also practice optimized therapy based on the results of genetic analyses routinely performed on tumor specimens obtained from glioma patients. Currently, using polymeric micelles, we develop a new mode of chemotherapeutic drug delivery system for brain tumors.

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 is presently the only one that can provide vagus nerve stimulation therapy in Japan, we are trying to evaluate its efficacy and establish its significance in epilepsy treatment. Efficacy evaluation and development of surgical

instruments has been promoting 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.

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 intracranial electrodes implanted in epilepsy patients. The latter is our markedly advantageous feature that enables us to obtain brain information with much higher spatial resolution and SN ratio. We are planning to expand the research on this field to the study on brain-computer interface in cooperation with other brain research laboratories and engineering laboratories.

5) Gamma knife radiosurgery

Our department is the first to introduce gamma knife radiosurgery in Japan to treat various kinds of intracranial lesions including skull base tumors or deep-seated brain arteriovenous malformations with successful clinical result. We have particularly excellent achievement on treatment of brain arteriovenous malformations; not only imaging result but also effect on the risk of hemorrhage was analyzed and reported in NEJM 352:146-53,2005. Moreover, the integration of diffusion-tensor tractography into gamma knife treatment enabled us to confirm the dose to the critical white matter fibers inside the brain, which can be performed only in our department among the world and can lead to safer treatment.

6) Clinical applications of the functional brain imaging for neurosurgery

Our department intensively utilizes various kinds of functional 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.

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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 including research fellows, graduate students and guest researchers in our department.

Teaching activities

The field of our department covers the wide area of preventive medicine. The main scope of 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 of public health issues, including health policy and economics, occupational medicine, community and clinical epidemiology, 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.

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 primary care, occupational and environmental health, infection and tuberculosis

control, mental health, international health, current health policy in Japan, 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 public 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 Health Sciences and Nursing, 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) Doctoral Program (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 several policy studies in terms of public awareness of medical technology. 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 developing countries, since such a system involves medical, behavioral, social, and economic factors, and would inevitably become an important health policy issue.

2) Occupational health

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

3) Community preventive measures

We have done several studies on preventive measures in a community, such as child immunization programs in rural China, and maternal and child health, and infectious disease control programs in Afghanistan.

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Social Medicine

2. Forensic Medicine, and Medical Informatics and Economics

Department of Forensic Medicine

Professor

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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 discovered the antigen-antibody reaction and complement fixation reaction.

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

The 4th Professor Shokichi Ueno discovered the complex III. 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 on the mechanism of ischemic heart disease and sudden cardiac death related to psychological stress, with respect to gap junction, intracellular signaling, and proteolysis. Additionally, the death investigation system on unnatural death and medical practice-related death is another topic of study.

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 80-100 criminal cases in eastern part of Tokyo every year. We have already autopsied more than 10000 cases since 1889. 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 1889. 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. 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.

Teaching activities

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 activities

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 mechanisms underlying sudden cardiac deaths due to ischemia or emotional stress

The Gap Junction (GJ) that is comprised of Connexin 43 (Cx43) contributes to synchronization of contraction and propagation of injury from cell to adjacent cell. It has been thought that down-regulation, translocation, or dephosphorylation of Cx43 is involved in the impaired conduction and arrhythmias.

- 1) Involvement of GJ in myocardial injury and lesion development in ischemic heart disease models... We found that contraction bands, frequently found in sudden cardiac death, are propagated from cell to cell through GJs with enhanced activity after enhanced incorporation of Cx43.
- 2) GJ formation and the contribution of its ischemic change to the development of injury and arrhythmias in cultured cardiomyocytes... Cultured cardiomyocytes are aligned in tandem with intercalated discs composed of translocated Cx43. In the system, we have undertaken to investigate the molecular mechanism of Cx43 turnover under baseline and ischemic conditions, and the contribution of Cx43-based GJ to injury propagation and arrhythmias.
- 3) Changes in GJ and its contribution to arrhythmogenesis in a restraint model... When excited persons are restrained, some of them suddenly die. We found that restraint induces Cx43 translocation to GJs in rats with a peak at 60 minutes, and that some portions of rats suddenly die of ventricular tachycardia/

fibrillation.

4) Changes in GJ and its contribution to arrhythmogenesis in pressure overloaded (perfused) heart model, and changes in the interaction of extracellular matrix (ECM), adhesion molecules, and cytoskeletons and its contribution to contractile failure in the same model...By use of the pressure overload model of perfused heart, we have tested whether pressure overload, related to accident or violence, induces arrhythmias. In fact, Cx43 is down-regulated in the pressure overload model. On the other hand, myocardial contraction is enhanced by pressure-overload. It has been thought that signal transduction and protein-protein interaction between ECM proteins, adhesion molecules, and cytoskeletal proteins contribute to the "enhanced contraction". We aimed to clarify the mechanisms underlying the arrhythmias and contractile failure under pressure-overload and emotional stress.

5) Contribution of oxidative stress to cardiovascular risks and arrhythmogenesis in the models of sleep apnea syndrome (SAS), and manic-depressive disease (MDD)...SAS and MDD have been a focus of research related to cardiovascular risks, but the mechanisms are largely unknown. We have undertaken to produce animal models, and investigate how SAS or MDD generates cardiovascular risks with reference to oxidative stress.

2. Investigation of legal-social systems related to death investigation system and patient safety

1) Study on disclosure of autopsy information and bereavement services...In order to resolve the disputes due to restricted disclosure of information on forensic autopsies, we have performed questionnaire studies, submitted recommendation from the study results, and adopted practical measures.

2) Study on investigation of medical practice associated deaths...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. For the new investigation system, we are trying to offer evidence and recommendation.

3) Study on presentation of expert opinions in jury (saiban-in) system...We have investigated how juries can understand the expert opinion without influence by emotional stress through computer graphic or other tactics.

3. Improvement of examinations in forensic practices
While examining each case, we have developed or applied new methods in our practices described below.

- 1) Development of new toxicological analyses
- 2) Development of new technique for racial or personal identification based on DNA polymorphism
- 3) Studies on estimation of weapon, and plankton chorology

4. Forensic pathology

We have reported rare cases related to clinical practices or medical practice associated deaths. Additionally, to explore how cardiovascular lesions develop and develop new diagnostic methods, we performed immunohistochemistry to confirm the experimental findings or find phenomena that initiate experimental studies.

- 1) Report and analysis of rare diseases or injuries
- 2) Study on histopathological diagnosis

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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 official 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, Prof. T. Kiuchi from UMIN center, Assoc. Prof. S. Oku from the Department of Healthcare Related Informatics that is the affiliated department, Assoc. Prof. H. Yasunaga from the Department of Health Management and Policy, 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 a 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

The department offers the Medical Science Doctoral course (4-year program). The eligibility for admission is open to those who graduate from a 6-year undergraduate program at the School of Medicine and those who have master's degrees either in the University of Tokyo or any other institutions. It does not need to have a medical license to apply for admission. Students will receive Doctor's degree in Medical Science with completion of required units and passing a doctoral thesis.

The department is collaborating with the health informatics course in the division of Health Sciences and Nursing at the Graduate School of Medicine. Although the department formally belongs to the Division of Social Medicine, it offers the course of health informatics for students in the division of Health Sciences and Nursing. Therefore most faculty members in this department also supervise the students in the Health Informatics course. The Health Informatics course offers 2-year master's course program and 3-year doctoral course program. Completing required units and passing thesis, the master's course students will receive Master's degree in Health Science and the doctoral course student will receive Doctor's degree in Health Science.

Furthermore our department accepts the students in the master's course of Medical Science.

In this master's course, all students spend the first four months on the planned coursework, then will decide which department they wish to be enrolled. After assignment of each department, students conduct their researches and complete master's thesis over remaining one and half year. Completing the required units and passing the thesis, they will receive the Master's degree in Medical Science.

The enrolled students in FY2008 are five in doctor's course for Medical Informatics and Economics, one in doctor's course for Health Informatics.

The students' researches cover various topics. The main ones are the analysis of medical cost for the DPC Classification", development of method for medical ontology, a study on the communication model between healthcare professionals and patients, a study on methods for healthcare safety control, medical support by electronic description format of chemical therapy regimen and inference mechanism, and so on.

Research activities

In 2008 F.Y., research staffs are Prof. Kazuhiko Ohe, Assistant Professor Kengo Miyo, Project Associate Hiroki Watanabe, Research Associate Izumi Yamaguchi, hiroo Ide, Takashi Noguchi, Katsuya Tanaka, and Project Research Associate Takeshi Imai, Megumi Sato, Shiro Matsuya, and Project Research Assistant Yuichi Yoshida, and Masayuki Kajino.

Our main 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) 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) A study on the development of a patient-oriented, event-driven, and intellectual clinical support subsystem (Industry-academia collaboration project with Fujitsu Limited, 2004-2009)

This research develops autonomic, distributed, real-time clinical support system. This system will be tested by being incorporated in the information system of the university of Tokyo Hospital.

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Internal Medicine

1. Medicine I

Department of Cardiovascular Medicine

Professor

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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 our 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 (outpatient clinic Nobukazu Ishizaka and hospital ward Hiroshi Yamashita), 15 research associates, 9 staff members, 23 graduate school students, 3 researchers, 1 members on leave and 2 members studying abroad.

Clinical activities

In 2008, 1,723 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 2,001 patients, of which 586 cases were interventional procedures. CT coronary angiography was examined in 328 patients and cardiovascular MRI in 99. For arrhythmias, there were 79 cases of implantation of a pacemaker, 84 cases of catheter ablation, and other specialized pacemaker devices such as 17 cases of implantation of a cardioverter-defibrillator, and 12 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 4 cases also in 2008. Duration of hospitalization is on average 12.3 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 in addition to hypertension and peripheral artery disease. Out-patient clinics are open both mornings and afternoons from Monday to Friday. Approximately 200 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, chart rounds, grand rounds and clinical conferences.

Research activities

Areas of interest are as follows:

1. Regulated expression of smooth muscle myosin heavy chain
2. Mouse genetic models of cardiovascular diseases and vascular development
3. Differentiation of smooth muscle cells
4. Genetic risk analysis of atherosclerosis
5. Mechanism of post-PTCA restenosis
6. MRI and CT in cardiovascular diseases
7. Gene expression and regulation in cardiomyocytes
8. Nitric oxide and endothelial function
9. Aerobic threshold and cardiac rehabilitation
10. Molecular analysis of myosin light chain mutations in familial hypertrophic cardiomyopathy
11. Clock gene in cardiovascular diseases
12. Early diagnosis of ischemic heart disease using visualization techniques of coronary arteries
13. Anti-arrhythmia therapy using catheter ablation
14. New treatment for pulmonary hypertension
15. Development of drug eluting stent
16. Clinical application of vasoactive substances for cardiorenal insufficiency
17. Bone marrow-derived cells in atherosclerosis
18. Regeneration therapy for cardiovascular disease
19. Diagnosis and treatment of Marfan syndrome
20. Mechanisms for cardiorenal association
21. Ischemic heart disease in patients with diabetic retinopathy

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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 research 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 15 respiratory physicians are doing clinical works.

The Department of Respiratory Medicine was established in April 1998. In June 2003, Takahide Nagase was appointed to Professor and since then chairs the Department.

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 lung diseases, 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 sever respiratory failure such as sever 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 over 10 years ago, 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 two years ago. 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. 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 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 2008

1. Primary lung cancer	278
3. Respiratory infection	113
2. Interstitial lung disease	44
4. COPD	39
5. Asthma	29

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, where radiological diagnosis, indication of thoracoscopic biopsy, CT-guided biopsy, and surgical and radiological treatment are discussed, making it possible to give best care to individual patients.

Teaching Activities

As for under-graduate education, our department takes part in systemic lectures and specific learning for diagnosis and treatment of respiratory diseases for the 4th year medical students, bed-side 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 systemic 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 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 bed-side 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. Lecture on fundamental chest radiology is provided by the respiratory specialists as one of essential elements in bed-side learning.

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 disease 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. Our program, in general, is highly appreciated by the students.

As for the post-graduate education, 8 to 9 junior residents join the Department of General Medicine on the 13th floor simultaneously for one to two months, and are expected to experience respiratory as well as other diseases. Since the training period is short, the residents are expected to experience emergency cases as often as possible.

Research Activities

Our department is conducting basic and clinical researches for many respiratory disorders including lung cancer, COPD, asthma, interstitial lung diseases, respiratory infections, acute lung injury, chronic respiratory failure and others. We have also been studying the effects of air pollutants such as diesel exhausts. 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 analysis of lung cancer in collaboration with the Faculty of the Department of Thoracic Surgery, cell biological analysis using airway epithelial cells, fibroblast, smooth muscle cells and lung cancer cells. Respiratory rehabilitation utilizing KAATSU training shows promising preliminary results. 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 disease-susceptibility genes in respiratory diseases

Effects of KAATSU training on respiratory rehabilitation

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

Analysis of signal transduction through EGF receptor system in lung cancer and its therapeutic application

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

Effects of air pollutants such as diesel exhausts on airway hyperresponsiveness

Elucidation of molecular mechanisms of tissue-remodeling, especially in relation to epithelial mesenchymal transition, in respiratory diseases

Roles of chemokines, cytokines and eicosanoids on functional regulation of airway epithelial cells, smooth muscles and fibroblasts

Elucidation of molecular mechanisms underlying the pathogenesis of pulmonary fibrosis

Elucidation of molecular pathogenetic mechanism of acute lung injury

Analysis of disease models using genetically engineered mice.

Takahide Nagase is an Associate Editor of *Respirology* and an Editorial Board Member of *American Journal of Physiology*.

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Introduction and Organization

The Department of Gastroenterology was established through a reorganization of the Postgraduate 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, pancreatobiliary and digestive canal. It is comprised of a professor, 3 lecturers, 17 associates, 11 fellows, 30 graduates and 11 other visiting researchers including students from abroad (March, 2009). 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 and fifth

floor of Ward B also takes important part for providing rooms of 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 97 inpatients on average, which is about 2,700 in total per year. We receive about 110 new patients in and out of the hospital each week, with an average hospital stay of 12.9 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 5,600 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. (1217 cases in 2008). 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 (108 cases in 2008). 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.

ERCP is performed more than 750 cases each year. The number of patients treated for choledocholithiasis with endoscopic papillary balloon dilation method exceed 1,000, which is possibly the largest in the world. Endoscopic metallic stenting is an effective palliative care for malignant obstructive jaundice (40 patients a year). Covered metallic stent placement has been performed in a total of 550 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 also performed for many challenging cases. ESD (endoscopic submucosal dissection) is performed as a curative endoscopic treatment for neoplasms in esophagus, stomach or colon (240 patients a year).

Endoscopic variceal ligations for esophageal varices (50 patients a year) are also frequently done. Double-balloon endoscopy and capsule endoscopy have been introduced recently, which enabled the examination of whole small intestines. All those interventions are performed by members of the department specially trained for each technique. Our strategy for the management of malignancies is interventional therapy and chemotherapy (180 cases for pancreato-biliary and 50 cases for digestive tract neoplasms).

On outpatient basis, ultrasonography is performed on 16,000 patients, gastroduodenal

endoscopy on 6,700, and colonoscopy on 3,500 patients each year, leading the detection of about 140 cases of gastric cancer and 170 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 bed-side teaching 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 as an oral examination. Students are also required to summarize and outline articles in 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 as a basic or clinical researcher. Currently, the department has 50 students who were graduated from more than 30 medical schools in Japan.

Research Activities

Since gastroenterology covers various organs and diseases, everything below the diaphragms except for the kidneys and the reproductive system, themes of a

research are virtually unlimited as shown in the list of publication described below. Both basic and clinical researchers are equally encouraged, on condition that the results may eventually contribute to the cure of gastroenterological disorders. For basic researches, the department has been eager to acquire cutting-edge methodologies, especially those in molecular biology and genetics. The themes of our recent basic researches include mRNA expression analysis using microarray, protein expression analysis using mass spectrometer, and gene mutation analysis using laser micro dissection of clinically obtained samples.

Various clinical activities are recorded in database and analyzed. Studies oriented for evidence-based medicine are highly appreciated. Recent randomized-controlled trials include interferon to prevent recurrence of hepatocellular carcinoma, evaluation of diagnostic usefulness of angiography with computed tomography, and radiofrequency ablation for liver metastasis of colorectal cancer. We have also designed clinical trials of TSU-68 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, additional mosapride in therapy of gastroesophageal 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

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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.

Division of Total Renal Care Medicine

Homepage <http://www.trc.umin.jp>

Introduction and Organization

Division of Total Renal Care was established in June 2004 by courtesy of TERUMO Co., a leading company in the field of continuous ambulatory peritoneal dialysis (CAPD), as a part of 22nd Century Medical and Research Center of The University of Tokyo Hospital. The main object of this division is to make it possible to provide the best total renal care for patients with end stage renal disease (ESRD).

Clinical activities

We are engaged in the care of patients undergoing CAPD, the creation of arteriovenous shunt for hemodialysis, and kidney transplantation in collaboration with nearby medical facilities.

Research activities

Two research projects are now ongoing. One is the investigation of changes of peritoneal function over time with special emphasis on histopathological alteration of mesothelial cells by peritoneal dialysate. Another one is to clarify the mechanism of renal preservation effect of angiotensin-II receptor blockers using cyclosporine-treated nephrotoxic rats.

Department of Clinical & Molecular Epidemiology

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

Introduction and Organization

The Department of Clinical & Molecular Epidemiology was established in June 2004 as an endowed department (Tanabe Mitsubishi Seiyaku Co.,

Ltd.) of the Graduate School of Medicine, the University of Tokyo. Our department also belongs to the 22nd Century Medical 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.

Division of Molecular Cardio- vascular Metabolism

Homepage <http://plaza.umin.ac.jp/~kid-endo/a-3-13.html>

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), Division of Molecular Cardiovascular Metabolism was started with donation of Daiichi-Sankyo Company, Ltd. in 2006.

Research activities

In basic research, we are investigating the role of reactive oxygen species (ROS), the sympathetic nervous system, and the renin-angiotensin-aldosterone system in the pathophysiology of salt-sensitive hypertension, metabolic syndrome, and their reno-cardiovascular complication. We are also conducting a clinical research investigating the renoprotective effect of some types of antihypertensives such as calcium channel blockers and aldosterone antagonists.

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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. Yukiko Okazaki), 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), 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 4000 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, excise therapy and medical therapy.

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

Teaching activities

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

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

In clinical lectures, we present clinical cases of important diseases such as diabetes mellitus, and try to discuss with the students several points for

planning the diagnosis and treatment in collaboration with the faculties of the Departments of Nephrology, Cardiology, and Ophthalmology.

During the period of 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. As of March in 2009, the staff of Department of Hematology and Oncology consists of thirty members including one professor, 2 lecturers, one special lecturer (hospital), and 5 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 are also discussed weekly in the clinical conferences, each focusing on hematological diseases, lymphomas, or hematopoietic stem cell transplantation. All these conferences are also attended by the staff member of Department of Cell Therapy and Transplantation because of clinical significance of hematopoietic stem cell transplantation in the treatment of hematological disorders.

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 1100 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.

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) proliferation and differentiation of hematopoietic stem 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, 15 graduate students for "Doctor of Medical Science" and 3 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. A professor, an associate professor, 6 guest lecturers, an associate, 8 graduate students and 15 full-time staff member 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 teaching 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

Kazuhiko Koike, Hiroshi Yotsuyanagi, Yoshizumi Shintani, Takeya Tsutsumi, Shuji Hatakeyama, Satoshi Itoyama, Takatoshi Kitazawa, Kuniko Ueda, Shu Okugawa, Miki Kawada, Shintaro Yanagimoto, Yohko Nukui, Katsutoshi Abe, Atsuhito Fukushima, Keita Tatsuno, Sohei Harada, Koji Goto, Mahoko Kamimura, Yusuke Yoshino, Takahiro Aoki, Koh Okamoto.

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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 2 senior residents, 6 graduate students, and 7 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 2008 January to 2008 December, 43 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

2008 January to 2008 December, the numbers of the new outpatients and of the overall outpatients in our department were 181 and 4294, 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 a clinical lecture on panic disorder 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-psychobehavioral 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

Professor

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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.
- 4'. Study on the mechanisms of transfusion related acute lung injury (TRALI) 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

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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 cystectomy or salpingo-oophorectomy (226 cases), laparoscopic hysterectomy or laparoscopically assisted vaginal hysterectomy (37 cases), laparoscopic or laparoscopically assisted myomectomy (97 cases), diagnostic laparoscopy for infertility (15 cases) laparoscopic surgery for ectopic pregnancy (20 cases), hysteroscopic surgery (52 cases) and so on, which make a total of 418 cases.

[Each number of cases indicates per year base.]

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 pro-gression 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 develop-ment.

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

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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 substrate 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 colorectal 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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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, 4 lecturers, 16 associates, 13 senior residents, 1 research fellow, and 13 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 growth 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 3,000g 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: Using extremely high grade oligonucleotide array system, many deletions and amplifications in unreported genes were identified in solid tumors including neuroblastoma, rhabdomyosarcoma and Ewing sarcoma. We identified over-expression of *ALK* gene in advanced stages of neuroblastoma.
- ② Nephrology group: Genetic and clinical diversity of Dent disease was identified in more than 90 unrelated patients. In the field of podocyte biology, novel mechanisms underlying the signal transduction via nephrin and neph1 were investigated.
- ③ Cardiology group: A novel intervention catheter technique in PDA was applied in several

congenital heart disease patients.

- ④ Immunology group: A therapy using human dendritic cells for children's cancer patients are performed.
- ⑤ Neonatology group: Clinical researches in the regulation of body fluid and circulation are being conducted.
- 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.

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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 staff are the chief professor, one associate professor, four research associates, two medical staff and three graduate students. More than 20 members of our department shoulder the clinical work as pediatric surgeons.

Clinical activities

Staff 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. The multiple functional forceps 3 mm in a diameter is developing for robotic surgery system at first.

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, and also started a fundamental study using an animal model.

Professor Iwanaka 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. Furthermore, The differentiation experiment of stem cells in amniotic fluid was performed in this laboratory by the obstetrics and gynecology department cooperation in our hospital.

The continuing tumor study group analyzes the genes related to tumor development. New therapy using a virus is under development.

The hepato-biliary and transplantation group elucidated the immune system after liver transplantation and small intestinal transplantation. They also studied the pathophysiology of clinical postoperative biliary atresia.

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Reproductive, Developmental and Aging Sciences

3. Aging Sciences

Department of Geriatric Medicine

Department of Aging Research

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Introduction and Organization

The Department of 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 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 respiratory, 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. Approximately 368 new and a total of 19,820 patients visit 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

Pulmonary unit

Lung mechanics, exercise physiology, management and assessment of dyspnea, sleep study for nocturnal disturbed breathing, latent virus infection in airways, animal model of aging lung, prediction and prevention of aspiration pneumonia, pathophysiology of interstitial lung disease, role of adhesion molecule in airway disease, role of endothelin, leukotrienes, and neuropeptides in asthma, proliferation and differentiation of lung fibroblasts, proliferation and apoptosis of airway disease, defensin and infectious disease.

Cardiovascular unit

Research on the mechanism and regulation of vascular calcification, sex hormone regulation of vascular function, clinical evaluation of vascular function using vascular ultrasound and pulse wave velocity, metabolic syndrome in the elderly.

Neurology unit

Diagnosis and treatment of the demented patients, neuro-protective function of Thioredoxin in *Drosophila*, regulation of apoptosis by stress-responsive kinases, etc

Osteoporosis and endocrinology unit

Bone metabolism, mechanism of action of nuclear receptors, genetic analysis of osteoporosis, vitamin K action, hormone dependent cancer.

Publications

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Surgical Sciences

1. Surgery

Department of Thoracic Surgery

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Associate Professor

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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 Masao Tsuduki 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 ~ 2008.3.31).

The Department of Cardiothoracic Surgery has been divided into two departments, Department of Cardiovascular Surgery and Department of Thoracic Surgery in 1998.

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 Fukami T), 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 280 surgeries are performed in the department in 2008.

Primary lung cancer has been the leading cause of death among the malignant neoplasms in our country. As the number of the dead patients by the lung cancer has been increasing, the basic and the clinical investigations for the treatment of the lung cancer are very important. In our department, the staffs participate the clinical works, studies and educations of diagnostics and therapeutics of the lung cancer as well as 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 cardiothoracic 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.

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) New methods for quantitative analysis of the DNA methylation of the lung cancer.
- (4) 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) Vaccine immunotherapy for the recurrent non-small cell lung cancer.
- (6) Mechanisms of acute or chronic rejection of the allogeneic lung and trachea.

Selected publications

- (1) Nakajima J, Murakawa T, Fukami T, Takamoto S. Is thoroscopic surgery justified to treat pulmonary metastasis from colorectal cancer? *Interact Cardiovasc Thorac Surg.* 7: 212-216, 2008.
- (2) Kawamura M, Nakajima J, Matsuguma H, Horio H, Miyoshi S, Nakagawa K, Fujisawa T, Kobayashi K; The Metastatic Lung Tumor Study Group of Japan. Surgical outcomes for pulmonary metastases from hepatocellular carcinoma. *Eur J Cardiothorac Surg.* 34: 196-199, 2008
- (3) Nakajima J, Murakawa T, Fukami T, Sano A, Takamoto S, Ohtsu H. Postthymectomy Myasthenia Gravis: Relationship with thymoma and antiacetylcholine receptor antibody. *Ann Thorac Surg* 86: 941-945, 2008
- (4) Babu AN, Murakawa T, Voelkel NF, Zamora MR, Henson PM, Nicolls MR. Functional microcirculation is lost in early airway fibrosis. *Proc Am Thorac Soc* 5: 371, 2008
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Department of Cardiothoracic Surgery

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Introduction and Organization

Cardiac surgery in the Department was initiated by Dr. Seiji Kimoto, who performed ligation of patent ductus arteriosus in June, aortic arch aneurysm resection in July and first-in-Japan Blalock-Taussig operation for Tetralogy of Fallot in October in 1951. He also started implantation of alcohol-preserved aortic homograft for abdominal aortic aneurysm in 1952, and closed commissurotomy for mitral valve stenosis in 1954. The first open heart surgery (atrial septal defect closure) was performed in 1955, using selective brain perfusion cooling method that was developed in the Department.

Establishment of Department of Thoracic Surgery in the University of Tokyo Hospital was approved by the government first in Japan December 15, 1964. Under the leadership of Professor Kimoto excellent research works were created especially on pacemaker and artificial heart, and many opinion leaders were

produced. Dr. Masahiro Saigusa, the second Professor, endeavored to make open heart surgery safer by introducing new-generation heart-lung machines to the Department. Dr. Kenichi Asano, the third Professor, started posterior-leaflet preserving mitral valve replacement first in Japan. He also dramatically improved surgical results of Tetralogy of Fallot. Dr. Akira Furuse, the fourth Professor, modernized management of extremely busy clinical works. During this time, the Department was divided into two Divisions, Cardiovascular and General thoracic, due to the University policy of Graduate-school.

Dr. Shinichi Takamoto assumed the fifth Professor in June 1997. He rearranged clinical teams into three groups (adult cardiac disease, thoracic aortic disease and congenital heart disease) to adapt the rapid progress of cardiovascular surgery. Present staffs are one Chief Professor, one Associate Professor and three 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 and Thursday. 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 400, 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 2009, eight cases of heart transplantation 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 every Saturday 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) new effective brain and spinal protection strategy, 2) intracardiac repair technique on a beating heart guided by three-dimensional echo, 3) basic and clinical research on cryopreserved allograft, 4) establishment of recovery and weaning protocols of left ventricular assist device, 5) a new technique of aortic valve sparing root replacement and its hemodynamic evaluation, 6) development of intrauterine treatment for fetal heart disease, 7)

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

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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 α in gastric
- 2) Molecular mechanisms of gastrointestinal tract cancer
 - Carcinogenesis
 - Clinical and experimental studies on the Barrett esophagus
 - 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. Ordinary, 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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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 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 1,500 from January 2008 to December 2008.

Elective operations are performed on Tuesday, Wednesday, and Thursday. A total of 1,400 operations

were performed in 2008. The numbers of main operations are adrenalectomy 12, radical nephrectomy 31, partial nephrectomy 15, radical cystectomy 15, radical prostatectomy 82, transurethral resection of the bladder tumor (TUR-Bt) 113, transurethral resection of the prostate (TUR-P) 21, and laparoscopic surgery 61.

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, and female Urology receive sophisticated care on the particular day of the week.

The total number of out-patients was approximately 30,700 patient-days from January 2008 to December 2008.

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 25 papers in English every year.

Renal tumor

Urolithiasis

Kidney Transplantation

Prostate diseases

New surgical technique

Urinary disturbance/ Female Urology

Andrology

Virology

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Introduction and Organization

In 1995, a new system for postgraduate education was introduced. The First Department of Surgery was reorganized to form the Department of Surgical Oncology and the Department of Vascular Surgery. The staff of the Department of Surgical Oncology consists of one Professor, two Lecturers and eight 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 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 specialities 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 2005, 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) Carcinogenesis in superficial early colorectal cancer
- 11) Genetic alterations in synchronous and metachronous multiple colorectal cancers
- 12) Microsatellite instability and a risk of developing multiple colorectal cancers
- 13) Dendritic cell Immunotherapy for advanced cancer
- 14) Cancer Immunotherapy targeting to the tumor vessels
- 15) Angiogenesis inhibition in peritoneal metastasis of gastric cancer
- 16) Role of LPA S1P and Edg receptors in tumor metastasis
- 17) Lipid metabolism in carcinogenesis and tumor progression
- 18) Role of peripheral nerve on the growth of gastrointestinal cancer
- 19) Genetic analysis on sensitivity to chemotherapeutic agents
- 20) Hemostasis and fibrinolysis in Oncology
- 21) Leptin and adiponectin in Oncology
- 22) Intraabdominal chemotherapy for peritoneal metastasis of gastric cancer
- 23) Angiogenic progenitor cells and antigen presentation
- 24) Fibroblast Growth Factor (FGF) in inflammatory bowel disease
- 25) Genetic analysis of undifferentiated colorectal cancer
- 26) High Frequency Ultrasonography (HIFU) for solid cancer
- 27) Endocannabinoid in anticancer therapy

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Department of Vascular Surgery

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Introduction and Organization

In 1995, a new system for postgraduate education was introduced. The First Department of Surgery was reorganized to form the Department of Vascular Surgery and the Department of Surgical Oncology. The staff of the Department of Vascular Surgery consists of one Professor, one Associate Professor, one Assistant Professor, 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,

angiography and intraoperative ultrasonography are available for the treatment of peripheral arterial disease. The outpatient clinic is open from Monday through Friday, and twenty-four-hour consultation is available for urgent or emergency problems.

The department was responsible for 197 surgically treated inpatients in the fiscal year of 2008. 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) Three-dimensional visualization abdominal aorta
- 2) Pathophysiology of the development of the aneurysm
- 3) Prevention of the anastomotic intimal hyperplasia
- 4) Pathophysiology of stent restenosis
- 5) Analyzing the intercellular transmission of the growth signal in the vascular smooth muscle cells
- 6) Tissue oxygen dynamics assessed by near infrared spectroscopy
- 7) Application of near infrared spectroscopy to blood flow monitoring during carotid endarterectomy
- 8) Development of a minimally invasive treatment modality for varicous veins of lower extremity using high frequency ultrasound.
- 9) Genome wide-association studies for arteriosclerosis.
- 10) Pharmacological analysis of microcirculation in in-vivo model
- 11) Mechanism of arteriogenesis in ischemic limb.
- 12) Development of a new drug delivery system for therapeutic angiogenesis
- 13) Introduction of gene into vascular wall cells by electroporation
- 14) Application of nano technology for in-vivo gene transfer to vascular wall cells
- 15) Basic research for arterialization of artificial organ
- 16) Development of a new method for evaluation of limb ischemia
- 17) Development of a new machine for auto-evaluation of in-vivo endothelial function
- 18) Creating strategy for diagnosis of acute aortic syndrome.

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Department of Metabolic Care and Endocrine Surgery

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Associates

Ei-ichi Tsuji MD. Kotoe Nishioka MD. PhD

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 endocrinological internal medicine and have about 60 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 endocrinological 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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Publications

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Surgical Sciences

2. Sensory and Motor System Medicine

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Introduction and Organaization

The Department of dermatology celebrated its 100th anniversary in 1990. Originally it was founded as the Department of dermatology and Urology, which also encompassed veneology. 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 professors, five lecturers and eight associates 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 dermatologist 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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Department of Plastic and Reconstructive Surgery

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Organization

The present faculty of the Department of Plastic and Reconstructive Surgery consists of 1 professor, 1 associate professor, 1 lecturer, 5 associates and 6 physicians. There are about 100 doctors in the department, including 16 medical trainees, 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 2,500 new patients and the total number of revisiting patients are about 25,000 in a year. In the operating theater over 350 operations are achieved under general anesthesia, while in the outpatient clinic about 350 operations are achieved under local anesthesia in a year. Each week, the professor goes the round of inpatients on every evening and Wednesday morning. Preoperative and postoperative conferences and seminar that all members of the department should attend are held at 6pm on Wednesday. The Journal club are also held at 8am on Wednesday and Thursday. Research conferences are held on every Monday and Friday evening.

Teaching Activities

In regard to pregraduate education, the department has the duty of lecturing to 2nd, 3rd 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. We have accepted 11 foreign and 32 Japanese visitors (in 2008) who desire to learn our new techniques, "supermicrosurgery".

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
- 17) Studies on regeneration of muscles
- 18) Studies on vascularized nerve flaps
- 19) Studies on microsurgery for lymphedema
- 20) Studies on preservation of cancer fertility

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Department of Oral-Maxillofacial Surgery

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Introduction and Organization

Department of Oral and Maxillofacial Surgery, commenced by Dr. Hisashi Ishihara in 1900, is one of the oldest departments in Graduate School of Medicine, the University of Tokyo. This department consists of wide variety of specialists, such as oral surgeons, orthodontists and prosthodontists. We handle all diseases in the oral-maxillofacial region, such as congenital anomalies, jaw deformities, benign and malignant tumors, trauma and inflammation. Dental care for the patients who have systemic disorders or under medical control is another field of our department. Multidisciplinary treatment teamed by these specialists is characteristic and has performed excellent results in clinical works. In research fields, all staffs participate in the clinical and basic research to support the treatment scientifically and to develop

new treatment protocols, and we have mainly performed the experimental studies on the regenerative abilities of tissues such as bone, periosteum, cartilage, perichondrium, vessels, nerve, and skin. At present, we are focusing on tissue engineering in research works especially in bone, cartilage and vessels. Professor Takato had established Tissue Engineering Division in the University of Tokyo Hospital and our department has 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 in 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. Carious 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 is 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) Distribution of cell cycle related 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-βFGF

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 German 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% 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 the top professor, two associate professors, four lecturers, 13 associates, six medical staff members, two visiting fellows, seven senior residents, and 12 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 neoplasms, 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 1-4 months. Since the training period is short, the residents 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 from April 2008 through March 2009.

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 are ward rounds by the professor on Tuesday. We have post- and preoperative case conferences on Monday evening, Tuesday morning and Thursday evening.

Eight hundred and eighty-nine operations were performed in 2008. These include 72 cervical and thoracic spine surgeries (including 19 computer-assisted surgeries (CAS)), 90 lumbar spine surgeries, 21 scoliosis surgeries (including 18 CAS), 68 surgeries for rheumatoid arthritis patients, 91 hip surgeries, 63 knee surgeries (including 19 CAS), 6 shoulder surgeries, 97 hand surgeries, 12 limb lengthening and reconstruction surgeries using external fixators, 122 surgeries for bone and soft tissue tumor and 90 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. The present professor Kozo Nakamura has also been the chief investigator of a national project to investigate OPLL. 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 have started 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 backgrounds of bone and joint diseases using forward and reverse genetics approaches
- 2) Signaling of differentiation and apoptosis of osteoclasts
- 3) Etiology of OPLL
- 4) Molecular background underlying the joint destruction by rheumatoid arthritis
- 5) Molecular background of osteoarthritis using a mouse genomics approach
- 6) Non-invasive evaluation of bone strength using a finite element method
- 7) In vivo bone formation by cytokines and its clinical application
- 8) Molecular mechanism of age-related bone and cartilage disorders
- 9) Molecular mechanism of glial cell differentiation

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. The fourth is founded in the Graduate School of Medicine and the researchers are developing durable artificial joints in cooperation with the Ishihara & 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).

In addition, we 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 4000 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 2400 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. Analysis of dynamics of aqueous flow
4. Drug effect on glaucoma
5. Screening method of glaucoma
6. Tissue engineering of the cornea
7. Clinical investigation of corneal shape
8. Gene therapy in corneal transplantation
9. Role of advanced glycation endproducts in ocular diseases
10. Clinical and basic research of excimer laser refractive surgery
11. Molecular analysis of retinal degenerative diseases
12. Color blindness and visual function
13. Electrophysiological analysis of the effect of drugs on the retina
14. Biocompatibility of intraocular lenses
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 810 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 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 & neck surgery, bronchoesophagology and rhinology and is related to case research, clinical statistics and clinical electrophysiology. Basic research is also encouraged to solve essence of clinical problems and to elucidate basic phenomena or anatomical and cellular structures. Our research topics cover:

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

implant and inner ear anomaly.

- 11) Hair cell physiology in the vestibular end organ.
- 12) Newborn hearing screening and language development in deaf children.
- 13) Physiology bone conduction innovation of bone conduction hearing and bilateral hearing.
- 14) Embryology of middle, inner ear and central auditory system.

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 2008, and six 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 150 patients corresponding about 15% 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
- 4) Analysis of motion and energy expenditure in the activities of daily living in the physically disabled
- 5) Non-invasive evaluation of lower limb motor

function in spina bifida

- 6) Evaluation of higher brain function in patients with spina bifida
- 7) Disabilities and handicaps in patients with skeletal dysplasias
- 8) Influence of physical therapy to skeletal muscles

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Surgical Sciences

3. Vital Care Medicine

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Introduction and Organization

The Department of Anesthesiology was established in 1952. 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 liver transplant, spinal/epidural anesthesia and monitored anesthetic care for electroconvulsion therapy. Recently, the number of high risk or geriatric patients is increasing. In addition, more

than 20% of the surgery (about 8000 cases in total 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 painful diseases. We also provide preoperative anesthetic consult service for patients who have various medical diseases. From April 2007 to April 2008, the number of ambulatory patients was about ten thousand; four hundred and forty 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 nine hundred and fifty 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 and the preliminary consideration, the mechanisms of anesthesia, inhalational anesthesia, intravenous anesthesia and circulation, the balance of body fluid, acid-base balance, muscle relaxants, the 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 technique of examinations and physiological- and pharmacological-knowledge which are essential for the management of 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 prepare a case report of anesthetic management and a paper on anesthetics and cardiovascular drugs in peri-operative use. We discuss the contents of the reports and papers with students at the end of bedside learning, for further comprehension.

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) Modification of immune system by anesthetics
- 4) Signal transduction pathway related to apoptosis activated by sepsis or ischemia-reperfusion insult
- 5) investigation of pathophysiology of shock
- 6) A role of lipid mediators in organ damage mediated by ischemia-reperfusion injury of a mouse lower limb
- 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

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Department of Emergency and Critical Care Medicine

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Homepage

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.

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 2004, we had about 6,000 ambulance patients out of total

17,000 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 1,000 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.

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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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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), 32 graduate students (14 master course students and 18 doctor course students) including 2 international students and 19 students qualified with nurse, and 3 research students. More than forty 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 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 2008, 7 MC students submitted Master Thesis and gained Master's Degree. Two DC students 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

Professor

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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, 10 doctoral course students, 7 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 special courses on mental health I and II, featuring occupational mental health and research methodology of epidemiology in mental health, respectively, in the fiscal year of 2008. 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

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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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Department of Biomedical Ethics & Department of Health Promotion Sciences

Professor

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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. 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, a total of eleven lecturers from other organizations, and fifteen 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. Seven bachelor theses, eight master theses, and six doctoral dissertations were completed between April 2004 and March 2009. 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://square.umin.ac.jp/CBEL/index.html>).

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

Publications

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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.

Lecturer

Minako Sasaki, Ph.D., R.N.

Assistant Professor

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

A. Graduate courses

1. 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.

2. 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.
3. 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.

4. 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.

B. Undergraduate Courses

1. 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).

2. 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.

3. 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.

4. 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.

5. 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.

6. 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.

7. 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.

1. 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.

2. 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.

3. 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.

4. 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

5. 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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8. Kanda K. Benchmarking for quality improvement of nursing service: Evaluation of quality of nursing service based on patient outcomes. *EB NURSING* 2008; 8(1): 88-93. (in Japanese)

Department of Family Nursing

Professor

Associate Professor

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Lecturer

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Research Associate

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Kafumi Sugishita, R.N., R.M., M.H.S.

Hiroe Yamamoto, R.N., R.M., M.S.

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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 five faculty members: an associate professor, a lecturer three research associates and a technical specialist. Also it has seven doctoral students, four master's course students, two research student, and thirteen 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
2. Undergraduate Courses, School of Health Sciences and Nursing
 - Family Nursing
 - Pathophysiologic Immunology
3. Undergraduate Courses of Nursing, School of Health Sciences and Nursing

Pediatric Nursing

Clinical Practicum in Pediatric Nursing

4. Undergraduate Courses of Midwifery, School of Health Sciences and Nursing
 - Midwifery III
 - Clinical Practicum in Midwifery

Research

Topics of our current research projects are as follows:

1. Studies of Post Traumatic Stress Disorder (PTSD) and other late complication among persons who experienced childhood cancer
2. Studies of perinatal mental health and childrearing support
3. Childrearing and self care of persons with mental disorders
4. The development of an instrument measuring the quality of life for children
5. Qualitative research to explore childbearing family formation process
6. A study of mourning work in the family bereaved children
7. Psychosocial factors related to symptom management of children with cancer

8. Families/siblings of children with chronic illness

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 three faculty members introduced above and 26 graduate course students (18 in master course, 8 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 Health Sciences and Nursing
 - 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.

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 methodology of community assessment for 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 activity model of public health nurse and terminology of community health nursing

We intend to standardize the terms used in community health nursing and develop the activity model for community health nursing (primarily for public health nurses). Through review and brainstorming, we will systematize the terms which explain the activity of public health nurses, develop the activity model, and verify the validity of the model.

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 and validating the check sheet to detect the patients who have the potential need of visiting nurse services.

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, making guidelines for multisectoral and interagency cooperation among 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, mother's loneliness and their relationship with the society, children's easiness of going to sleep and mother's fatigue. Also, the network for childrearing was investigated to avoid 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 2008 are 1) Care for older people with dementia at mealtimes in group-home, 2) Knee joint pain in older people and their health action, 3) Self care ability of the members of cardiac disease patients after operation and social support and 4) Acceptance to diseases and experiences in hospitalization for tuberculosis patients

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Health Sciences and Nursing

3. Clinical Nursing

Department of Adult Nursing / Palliative Care Nursing

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Lecturer

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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 effectiveness. Now we are planning to engage this strategy more widely, especially on the health testing system. Meanwhile we have been developing diabetes diet / physical activity-related QOL Scale.

Cardiovascular diseases: We have developed and validated Japanese version of the European Heart Failure Self-Care Behavior scale and Coronary revascularization outcome questionnaire, and investigated the factors associated with each outcomes which were measured by them. Furthermore, a follow-up study, evaluating the influence of the self-care on the rehospitalization has been conducted. We are on the process of developing a disease management program aimed to facilitate patients' self management. We also conducted a study about adult congenital heart disease.

Liver / pancreas diseases: To improve Quality of Life (QOL) of patients with pancreatic or primary liver cancer, we are starting the development of Japanese version of the disease-specific QOL questionnaires of EORTC designed for use in cancer clinical trials internationally. After the development of Japanese version, we will explore the factors relating to their QOL.

Neuromuscular diseases: In neurological conditions, pain is an extremely common feature but is often less precisely described. We showed apart of the actual conditions of pain and management of pain in patients with neuromuscular disease.

HIV/AIDS: We are on the process of research which investigates structure and barriers of HIV/AIDS related self care aimed to develop self care support tool.

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. The University of Tokyo Hospital is a medical facility that provides one of the highest levels of treatment in living donor liver transplantation and bone marrow transplantation in the

world. Therefore, we have conducted the following studies on cases at the hospital:

We have described the QOL of patients who underwent adult living donor liver transplantation, and the experiences of donors before and after transplantation. In addition, we initiated a study regarding difficulties in the chronic stage following bone marrow transplantation and support for reducing such difficulties.

We have also contributed to establish donor coordination system in the hematopoietic stem cell transplantation (HSCT) through the project which develops 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 have performed nation-wide surveys which aim to clarify the effectiveness of nurse specialist assignment, and have been conducting educational activities regarding the promotion of nursing activity in outpatient care.

4) Evaluation of Specialized Palliative Care and Quality Assurance

Palliative care services in Japan are primarily provided by palliative care teams in general wards, in palliative care units, and at home. We have conducted research on methods for evaluating palliative care services by focusing on various categories, such as symptom control and communication. We have developed a Japanese version of the STAS-J, which is an evaluation scale developed in the U.K., and are attempting to promote its utilization. We have participated in the development of a care evaluation scale for bereaved families. Furthermore, we are conducting a survey on the current status of palliative care teams, and research regarding the evaluation. We are also strongly motivated to evaluate palliative care for patients with hematological cancers, which remain

uncommon in Japan.

5) Continuity of the Palliative Care System

End-stage cancer patients receive care in general wards, palliative care units, and at home. We have conducted a study on the preparation of a system for transition in the care setting. Actual research goals include the identification of preference in care settings and related factors, and the factors that facilitate a smooth transition from general wards or palliative units to the patient's home.

6) Good Death in Japan

Recently, the conceptualization of good death, which is one of the goals of palliative care, and investigations of the current status are being conducted in Western countries. We have conceptualized good death in Japan by conducting qualitative research, followed by quantitative research, on groups comprised of the general public and bereaved families. Furthermore, we have established intervention measures by investigating the attainment of good death and possible barriers. We also consider that it is important to provide education for the general public.

7) Palliative Care at Home

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.

We have conducted a study regarding the actual care provided at home based on a survey of patients and their families, and a study that described and evaluated the experiences of bereaved families who attended the home death. We also take part in the project which aims to establish regional palliative care system.

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Department of Midwifery and Women's Health

Professor

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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, 7 graduate students (4 in master course, 3 in doctoral course), and 2 research students.

Teaching activities

We teach 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)

4. Master's thesis

The followings were research themes in 2008;

- 1) The relationship between functions of transverses abdomens/pelvic floor muscles and stress urinary incontinence in postpartum women.
- 2) The relationship between the maternal plasma total homocysteine levels and the birth weight.
- 3) The prospective study of relationships between breastfeeding and postpartum depressive symptom from 1 month to 5 months postpartum.

5. Doctoral thesis

The following was a research theme in 2008;

- 1) Longitudinal changes in the relationship between oxidative stress and lifestyle factors throughout pregnancy.
- 2) Appropriate Gestational Weight Gain by Body Mass Index for Lowering Perinatal Risks: a Population-based Study in Nha Trang City, Khanh Hoa Province, Vietnam.

Research activities

Our research activities focus on maternal-child health care as well as promoting the health and quality of life of women at each stage of the life cycle.

Current research projects are as follows.

1. Basic research for the efficacy of perinatal care.
 - 1) Nutrition and weight management during pregnancy and postpartum.

To evaluate the supervision of pregnant women in outpatient care and to investigate methods for controlling the mother's body weight, nutritional intake, physical activity, and weight change during pregnancy in order to optimize the management system.
 - 2) Lifestyle and oxidative stress during pregnancy.

To identify the biochemical parameters such as oxidative stress markers for the assessment of a healthy lifestyle during pregnancy.
 - 3) Maternal body composition during pregnancy and infant birth weight

To identify the optimal weight control method and lifestyle during pregnancy for the prevention of low birth weight via the measurement of weight, body composition, lipid metabolic biomarkers, daily lifestyle, and nutritional intake.
 - 4) Determination of the appropriate gestational weight gain by body mass index for lowering perinatal risks.

To study the association between pregnancy weight gain among Vietnamese women with varying prepregnancy body mass indices and the risk factors for adverse perinatal outcome.
 - 5) Physical activity during pregnancy.

To assess the reliability and validity of the Japanese and Vietnamese versions of the

pregnancy physical activity questionnaire (PPAQ).

- 6) Sleeping posture and sleep problems of pregnant women.

To study the relationship between sleeping posture and the quality of sleep, the state of respiration and the circulatory system.
- 7) Changes in the prostaglandin levels in saliva during pregnancy, labor and the postpartum period.

To examine the changes in the prostaglandin levels in saliva during pregnancy, labor and the postpartum period.
- 8) Promotion of women's health care after delivery.

To study the relationship between maternal body weight or body composition and life-style factors among postpartum women.

2. Perinatal care program development and evaluation.
 - 1) Determine the effectiveness of an exercise program for promoting mental health in postnatal women: a randomized controlled trial.

To evaluate the effectiveness of the postpartum exercise program on mental health.
 - 2) Change in the skeletal and muscular system during pregnancy and postpartum.

To describe the function of the skeletal and muscular system during pregnancy and postpartum, and to develop a perinatal physical self-care program for the prevention of minor troubles.

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 5. Ryoko Murayama, Kazuo Aoki. A Change of Sleep Posture with Pregnant Progress and Influence to Respiration and Circulatory System. *Stress Science Research*. In press. (in Japanese)
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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, 4 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 monthly journal clubs and study clubs.

Research

Our research field covers mental health and psychiatric nursing. Our department has many research projects across diverse fields as follows: study of community support system for the people

with mental health needs; issues of caregiver burden in family caregivers; psychiatric clinical pathways; behavioral and psychological symptoms of dementia; patient satisfaction with psychiatric services; practice and evaluation of home visiting psychiatric nursing; illness self-management in mental health; and recovery for people with mental health difficulties. We are conducting studies in collaboration with researchers in other institutions and universities.

Publications

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Department of Gerontological Nursing / Wound Care Management

Professor

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Introduction and Organization

The Department of Gerontological Nursing was established in June 2003, followed by the establishment of the Department of Wound Care Management in April 2006. These two departments are currently headed by 1 professor and assisted by 1 project lecturer and 2 research associates, and 2 part-time lecturers for undergraduate course and 5 for graduate course. The student body consists of 4 doctoral course students, 12 master course students, and 3 research students. The goal of our department is to achieve “Evidence-based practice and development of gerontological nursing and wound care management”, where we are striving to develop new techniques, instruments, and assessment skills in accordance of nursing science and engineering and clinical nursing.

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. The main themes in the 2008 curriculum were as follows;

- a) Practical simulation for gerontological nursing
- b) Physical, psychological & social characteristics of the elderly
- c) Social, health and medical policies for a healthy life of the elderly
- d) Health and nursing of the elderly (gait disorder)
- e) Health and nursing of the elderly (pressure ulcer)
- f) Health and nursing of the elderly (dementia)
- g) Health and nursing of the elderly (critical care, rehabilitation, and end-of-life care and its ethical issues)

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 2008 curriculum were as follows;

- a) Feeding and swallowing difficulty of the elderly
- b) Aging and dementia
- c) Age-related changes in the physiologic system
- d) Aging and osteoporosis
- e) Aging and cardiovascular disorders

- f) Aging and respiratory disorders
- g) Aging and renal function, hypertension, and stroke
- h) Pharmacologic management of the elderly
- i) Nutritional management of the elderly

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

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

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

3) Bachelor's thesis

N/A for this year.

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 latest developments related to gerontological nursing.

Gerontological Nursing I offers review and critical analysis of latest world-wide researches around gerontological nursing. The main theme in 2008 was to discuss the ideal situation in the geriatric medicine by comparing insurance systems around the world through journal club. Related lectures were also provided, 1. Nutritional management of the elderly, and 2. Geriatric medicine in community setting.

Gerontological Nursing II provides lectures and discussion regarding the recent topics around gerontological nursing, in which the main themes in 2008 were as follows;

- a) Influence of social activities and leisure time of care giver on the perceived care burden.
- b) Strategies for improving quality of nursing regarding visiting nurse, physical restraint, and nursing certification system
- c) Elderly needs during a natural disaster
- d) Nursing care for the younger demented people and their family

- e) Regeneration system of the hair follicle stem cell
- f) New style of home care for the highly impaired elderly

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

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

The course program focuses on understanding and the development of the practice, research, education, and perspectives in advanced wound care management.

Wound Care Management I offers review and critical analysis of latest world-wide researches involving wound care management. The main theme in 2008 was the topics on management of lymphoedema. Lymphoedema decrease QOL in the post-surgery patients, thus adequate management is required. The representative text for lymphoedema management was used to learn the basics and its management of lymphoedema.

Wound Care Management II provides lectures and discussion regarding the recent topics involving wound care management in critically ill patients, and the main themes in 2008 were as follows;

- a) Mechanisms of physical response to the severe invasion
- b) Respiration management of critically ill patients
- c) Management of stoma and fistula
- d) Wound management in the emergency unit
- e) ICU nursing
- f) Pressure ulcer management in acute spinal cord injured patients and pressure ulcers

5) Master's thesis

The followings were research themes in 2008;

‘Do nutritional markers in wound fluid reflect pressure ulcer status?’

‘Inoculation of *Pseudomonas aeruginosa* to the full-thickness wound surface induces delayed wound healing without inflammatory signs and symptoms in rats -Possibility as an animal model for critical colonization-’

‘Evaluation of pressure redistribution in new dynamic cushion for elderly’

‘Development of the Research Awareness Scale for Nurses’

‘Hypoxia is involved in deep tissue injury formation in a rat model’

6) Doctoral thesis

The following was a research theme in 2008;

‘Investigation of the role of the quorum sensing system on the establishment of pressure-induced ischemic wound infection by *Pseudomonas aeruginosa*’

Research activities

1. Activity policy

Our main activity involves the “Evidence-based Practice for Gerontological Nursing and Wound Care Management” where we are striving to develop new nursing techniques and instruments to fulfill the needs of those elderly wishing to maintain their independence.

Specifically, we are trying to improve the prediction, prevention, diagnosis, and treatment of elderly suffering with geriatric syndrome, pressure ulcers, diabetic foot ulcers, incontinence, malnutrition, pain, depression, and dementia. Most research is conducted under industry-academia cooperation. We hope through such researches to be able to increase physical activity and enhance self-esteem of the elderly in order to maintain their independent lifestyles.

2. Research fields and themes

1) Basic experimental studies

- Histological studies of terminally-ill patients skin
- Effect of vibration on blood circulation
- Cutaneous wound healing and DM
- Infection control based on quorum sensing signaling regulation
- Modeling of deep tissue injury in rats

2) Nursing engineering

- Effect of vibration on blood flow acceleration
- Development of new air-mattress equipped with interface pressure sensing system
- Development of self-regulating alternating air pressure cushion
- Quantitative evaluation of skin texture based on computed image analysis

3) Clinical studies

- Infection control of pressure ulcers
- Evaluation of low frictional dressing for pressure ulcer prevention
- Cross-sectional study of diabetic foot ulceration and its risk factors
- Evaluation of new diaper for elderly people for incontinence related dermatitis management
- Cross-sectional study of skin vulnerability of elderly patients requiring 24-hour diaper
- Qualitative analysis of competency and career development of WOC nurse
- Quality assessment of nursing ward in tertiary hospitals using pressure ulcer prevalence as an indicator

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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 programmes 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, 13:30-15:00 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 Grants

Epidemiology of HIV/AIDS: A cohort study and meta-analysis
Research on HIV/AIDS,
Health and Labour Sciences Research Grants

Genetic analysis of tuberculosis epidemiology
Scientific Research (B)
Grants-in-Aid for Scientific Research

Assessment of post-traumatic stress disorder among

earthquake survivors in Pakistan,
Research Grant Program (Two-Year Project),
The Toyota Foundation

Publications

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2. Sasaki Y, Ali M, Kakimoto K, Saroeun O, Kanal K, Kuroiwa C. Predictors of exclusive breastfeeding in early infancy: A survey report from Phnom Penh, Cambodia. *Journal of Pediatric Nursing*. 2009 (in press)
3. Vandan N, Ali M, Prasad R, Kuroiwa C. Physician's knowledge assessment in tuberculosis management in Lucknow, India: A public-private sector comparison. *Public Health*. 2009 (in press)
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5. Aiga H, Matsuoka S, Kuroiwa C, Yamamoto S. Malnutrition among children in rural Malawian fish-farming households. *Trans R Soc Trop Med Hyg*. 2009 (in press)
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8. Putthakeo P, Ali M, Vilayhong P, Ito C, Kuroiwa C. Factors influencing breastfeeding in children below 2 years of age in Lao PDR. *Journal of Pediatrics and Child Health*. (in press)
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24. Furuta M and Mori R. Factors affecting women's health-related behaviours and safe motherhood: A qualitative study from a refugee camp in Eastern Sudan. *Health Care for Women International*. 2008;29(8):884-905.

Department of Community and Global Health

Professor

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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 the nations. By bring together clinical, public health and social science research, we aim at:

1. Investigating how to improve health status of the most vulnerable people, in particular, in developing countries,
2. Undertaking research on the influence of globalization on health and social development,
3. Investigating mechanisms to reduce inequalities between and within nations on health and development.

The name of the department has been changed from “Department of International Community Health” to “Department of Community and Global Health” in April 2009. Our research will place more emphasis on how to activate community-based activities and how bottom-up approach can be linked to national or international policy. Our department

consists of: Professor (1), Assistant Professors (3), Visiting Lecturers (8), PhD course students (18), Master’s course students (24), Research students (5), and Visiting researchers (17).

International Cooperation Activities

Our department has conducted a variety of international cooperation activities. We have worked for Toyako G8 Summit as a member of Takemi Working Group from the end of 2007 to 2008 and attended a series of meetings as follows:

- Trilateral Commission Plenary Meeting - Presentation of Working Group draft paper "Global Health as a Human Security Challenge" (April 26, 2008)
- Brookings Institution Roundtable - "Challenges in Global Health and Japan's Contributions: Preparation for the G8 Summit" (April 28, 2008)
- Council on Foreign Relations Seminar - "Global Health and the G8" (April 29, 2008)
- International Conference on Global Action for Health System Strengthening (November 3-4, 2008)
- *G8 Hokkaido Toyako Summit Follow-Up Dissemination Seminar in Asia - Global Action for Health System Strengthening* (January 27, 2009)

In addition, we are working as an advisor for Filariasis control program of the WHO South-East Asia Regional Office. We also provide technical support to projects run by the JICA and NGOs in Lao PDR, Thailand, Vietnam, and Brazil, and conducted research in collaboration with the Cambodian government.

Teaching Activities

The objectives of our teaching activities are summarized as follows:

1. Train those who are willing to work for international cooperation in future,
2. Train those who are willing to contribute to carry out research in international health,
3. Teach general students who are interested in international health.

The major topics for teaching is as follows: 1) Global health, 2) Health promotion 3) School health in developing countries, 4) Community-based health interventions 5) Social Capital, 6) Research ethics, 7) Medical Anthropology, 8) Reproductive health

Our department has accepted students of various disciplines: medical doctors, nurses, co-medical workers, social scientists and others. The academic year of Master Course (MA, 2 years) and Doctor Course (PhD, 3 years) starts in April and ends in March every year. All the lectures and seminars are conducted in English.

Research activities

We have carried our research by working together with different international organizations, NGOs, universities in developing countries. The major focus of research has been primary health care, health promotion, school health, health and human rights (including migrants' health), conflict and health, injury prevention, HIV/AIDS, tuberculosis, malaria, leprosy, etc, in South and South East Asia.

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International Health

2. International Biomedical Sciences

Department of Human Genetics

Professor

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Associate Professor

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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, 12 graduate students, 2 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) Development of methodologies for the analysis of protein interactions.
- 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, sixteen visiting researchers, sixteen graduate students (including seven overseas students) and two research fellows.

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) Studies on developmental brain disorders caused by abnormal intracellular signal transduction, such as tuberous sclerosis, Noonan syndrome and Costello syndrome.
- (2) Clinical, genetic and pathologic studies of acute encephalopathies: Acute necrotizing encephalopathy and acute encephalopathy with febrile convulsive status epilepticus.
- (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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Introduction and Organization

We had four research/teaching faculties in FY2008. Apart from the faculty staffs, two secretaries, four doctoral candidates (three foreign students), six master course students (including two foreign students), and three research fellows are working in the department. There are nine 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.

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. 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 projects conducted in the past two years.

1. Neurodevelopmental effects of perinatal exposure to environmental chemicals:

Modern human societies, regardless developed or developing, consume and are exposed to a variety of chemical substances, which would be regarded as a substantial part of the environment. Since often the fetus/newborn is said to be relatively sensitive to these chemicals, we focused on the exposure to chemicals during perinatal period. Collaborating with several institutes/universities, we have conducted studies on the effects of heavy metals (mercury and cadmium), toxicity of which were still being debated in Japan and other countries, as well as those of so called endocrine disrupters. Toxicity was evaluated at cellular as well as organism levels, and major findings included susceptibility of metallothionein knock-out mice to the neurodevelopmental toxicity of metals. In this fiscal year, the effects of low-dose mercury and cadmium were reported, focusing on delayed effects of perinatal exposures. The effects of cadmium on the cultured neurons were examined using proteomics; non-monotonous dose-effect relationships were found and reported.

2. 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. In this fiscal year, surveys in each of the targeted countries was completed, and the analyses of the collected samples has been done, while some of the chemical analyses are still going on. Many unexpected chemicals were found in the biological samples, demonstrating the “invasion” of industrial potentially hazardous chemicals to rural communities of developing countries. In addition, substantial between-community difference in the chemical exposures was revealed. Final report of the project was submitted to the Ministry of Environment, Japan.

3. 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.

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. Effects of arsenic on children was examined and analyzed with regard to the relationship between arsenic toxicity and nutritional status. In the lowland Nepal, located upper-stream of the Bangladesh, relationship between the nutritional status and the arsenic toxicity was also examined. From both of these surveys, a distinct sex-related difference and the

effect of nutritional status on the arsenic toxicity were observed and reported.

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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 fal ciparum*,
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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School of Public Health

1. Epidemiology and Health Sciences

Department of Social and Preventive Epidemiology

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Lecturer

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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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Department of Health Economics and Epidemiology Research

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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 4 courses, two on clinical epidemiology and the other two 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. The Department has not yet accepted a doctoral student for the fiscal years of 2007-8, though two department faculties already contribute as thesis advisors for students in other tracks. The Department will be open to doctoral students who are interested in health economics and health services research since the year of 2009.

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. Several questionnaire tools for evaluating patient's quality of

life have been developed and validated in the area of orthopedic surgery. In the collaboration with the Department of Health Management and Policy in 22nd Medical Research Center in the University of Tokyo Hospital, the Department also contributes 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 association between income distribution and regional health status are widely acknowledged across countries including this country, yet the mechanism is still a matter of debate. The Department has contributed to an ongoing research of socioeconomic status and health among elderly population in the collaboration with the School of Economics of the University of Tokyo and the Research Institute of Economic, Industry, and Technology.

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 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 groups: professors and associate professors.

Whereas health communication is a major discipline in the USA and there are many such graduate programs, our department offers one of only two health communication programs in Japan. However, the importance of the health communication discipline is gradually becoming recognized academically and throughout society.

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. General Aspects of Health Communication
2. Social Marketing
3. Mass Media and Communication
4. Internet Communication
5. Edutainment
6. Science Communication
7. Hospital Management and Communication
8. Public Health Informatics
9. Communication During Emergency and Disaster
10. Publicity in Healthcare organizations
11. Provider-patient Communication
12. Communication Among Healthcare Consumers

[Health Communication Practice]

1. Research, Analysis and Evaluation of Websites
2. Website Development
3. Practice of Media Publicity
4. Evaluation of News
5. MBTI (Myers-Briggs Type Indicator)
6. 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 two main characteristics of research studies conducted through the Department of Health Communication, which distinguish them from studies at other medical informatics programs, are the following:

- (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 research studies 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 in 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) Technological Assessment of Health Information and Communication Technologies
Although information technology is expected to play an important role in healthcare, its comprehensive usefulness, including cost-effectiveness, has been rarely evaluated. We conducted a literature review in

2003 and concluded that there were few cost-effectiveness analyses for telemedicine programs even though many telemedicine programs have been implemented throughout many developed countries, including the USA and Japan. Based on the review, we have done a cost-effectiveness analysis for information technologies.

- (3) Edutainment Research
To disseminate clinical knowledge and information to laypersons, it is important to consider standards such as “easy to understand” and “acceptable by unknowledgeable persons.” We focus on studies related to media, entertainment, and interface design. For example, we have conducted the development and evaluation of edutainment tools for health education aimed at type-1 diabetes patients, as a concrete application.
- (4) Research Regarding Medical Management
It is important to make proper judgments and decisions in order to achieve optimal outcomes, a process which is termed “management.” However, scientific research and evaluations related to patient safety, quality improvement and medical management have not been well established in Japan. We focus on the Theory of Constraint (TOC) as a tool for medical management from a perspective of information utilization, and conducted research on medical error prevention and quality improvement.

- (5) Research Related to UMIN Activities
Most systems developed at the UMIN Center have been subjects for research. In particular, we published and reported systems utilizing advanced technologies and having scientifically meaningful concepts at academic conferences.

- (6) Information Systems for Clinical Epidemiologic Studies
We have developed and applied information systems for clinical epidemiological studies. Recently, we have focused on research in electronic formats and standardization that are related to clinical research, such as the Clinical Data Interchange Standards

Consortium (CDISC). We utilized the achievements attained by the medical research data center at the UMIN.

(7) Research Regarding the Security of an Information Network

The study addresses a Virtual Private Network (VPN), and secure transactions with electronic mail (encryption), which have been also utilized for system management at the UMIN Center.

(8) Research Plan Development; A Statistical Analysis of Clinical Studies

In cooperation with clinicians, we have developed clinical research plans and support statistical analysis. In addition, we have done data mining research for information extraction, knowledge discovery and prognostic modeling. Furthermore, we have conducted research and development for decision support systems to utilize the results in clinical practice.

(9) Patient Registry System for Quality Improvement

Many data have been accumulated in the existing hospital information system, such as electronic record systems; however, these data have not been utilized significantly for quality improvement, patient safety or medical management. We have deployed an interactive web-based patient registry system with a real-time feedback system of quality indicators (QIs).

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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, 31 visiting researchers and 10 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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3. Health Services Sciences

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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. This has just started. 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

The Department of Pharmacoepidemiology was set up in 1993 as a temporary department endowed by a pharmaceutical company (Rhone-Poulenc Rorer) with a time limit of 3-year period. The department has been further renewed five times in 1996, 1999, 2002, 2005 and 2008 as a department endowed by 15-20 pharmaceutical companies located in Japan. Currently, the Department of Pharmacoepidemiology has 1 professor, 2 associates and some assistants. The department also has a dozen of part-time workers.

Teaching activities

As in other endowment departments in the university, the department has no formal course of lectures to which it is responsible. However, the staff in the department has often made the lectures on pharmacoepidemiology and relevant issues. Such special lectures in the University of Tokyo include: (1)those in a lecture course of “pharmacology” for medical undergraduates and (2)those in a lecture course of “pharmacology and toxicology”

From 2006, the department has played the major roles in organizing and operating “pharmacoepidemiology seminars” sponsored by the Union of Japanese Scientists and Engineers (JUSE) (http://www.juse.or.jp/e/education_training/02_conventions.html). In the seminar, participants who come from drug companies, academia and regulatory body

learn various aspects of pharmacoepidemiology including the basic concepts of pharmacovigilance, signal generation, study design, analysis of data and related topics including pharmacoconomics. The course consists of 2 days per month for 6-months..

Research activities

To conduct epidemiological researches, the department has close association with the non-profitable organization (NPO) Drug Safety Research Unit Japan (DSRU Japan) which was established in 2001. The NPO is important to provide various functions needed to conduct large scale studies.

This NPO had a key function in many studies which the department conducted. For example, the NPO worked as the study office of pilot studies of Prescription-Event Monitoring in Japan (J-PEM) in late 1990s and also played the role of the study office of case-control study for the association between Non-steroidal inflammatory drugs and upper gastrointestinal bleeding of which the results were published in *Eur J Clin Pharmacol* in 2006.

One of the current main projects done by the department with the co-operation of the above NPO is Japan Statin Study (JSS) sponsored by the Public Health Research Foundation and directly conducted by Japanese Society for Pharmacoepidemiology (JSPE) and Scientific committee of Japanese Society of Hospital Pharmacies (JSHP). In JSS, currently more than 60 hospitals participate and identify the

study subjects using electronic prescription records in the hospital. In JSS, the design of case-cohort study is used and adverse muscle events (increase in CPK and rhabdomyolysis), hepatic events (increase in AST and ALT) and renal events (hematuria, proteinuria and increase in serum creatinine) are compared between the users of 6 kinds of statins currently available in Japan (pravastatin, simvastatin, fluvastatin, atorvastatin, pitavastatin and rosuvastatin). The design of case-cohort study is cost-effective suitable when studying multiple events and this study could be one of the prototypes for the future post-marketing comparative observational studies sponsored by drug companies. The above NPO plays the role as the study office of JSS as well.

Another study is on "Incidence of interstitial lung disease, myelotoxicity associated with chemotherapeutic agents and factors related to survival in patients with malignant mesothelioma: a retrospective cohort study in west part of Japan". In this study, more than 300 patients of malignant mesothelioma were identified and the incidence of interstitial lung disease, one of the major adverse events associated with anti-neoplastic treatments in Japanese population, incidence of other major adverse events including those due to myelotoxicity as well as survival of patients with mesothelioma are studied. The study will provide the baseline incidence of ILD in patients with mesothelioma, which will give an important information in evaluating the adverse events associated with the future study of patients with malignant mesothelioma.

The data-mining methodology for spontaneous reports has been adopted and routinely used in various administrative agencies in the Western countries and World Health Organization. Japanese administrative agency is also currently trying to introduce this new methodology. Currently, in the department an efficient new methodology is being studied where the data of Drug Use Investigations (DUIs) are used. The DUIs are cohort studies of thousands of patients using the new product without a comparator group conducted for about 30 years by a large number of drug companies as a legal duty for years.

In the Western countries as well as in Korea and Taiwan, pharmacoepidemiology studies are normally

conducted using large databases including claims database. In Japan the construction and use of database of monthly claims (called as "Rezepts") are taking place. To give an efficient way of the use of such claims database, a similar but smaller claims database currently available and provided by Japan Medical Data Center (JMDC) are analyzed. The JMDC data are used to estimate the relationship between anti-hypertensive drugs and the incidence of diabetes mellitus.

In the recent years, as the field associated with pharmacoepidemiology, the "therapeutic risk management" including risk minimization action plans (often abbreviated as RiskMAP) has been recognized as an important issue. A typical drug class requiring RiskMAP is teratogenic drugs. Thalidomide has been imported by individual doctors in Japan for the treatment of multiple myeloma since around 2000. Thalidomide is one such teratogenic drug requiring RiskMAP. The department has developed "safety management system for unapproved drugs" abbreviated as SMUD as the study supported by the Ministry of Health, Labour and Welfare between 2005 to 2008 with the support from UMIN center located in the Tokyo University Hospital. The SMUD will be operated sometime in 2009 by the MHLW which will assign some body to conduct SMUD under the service contract with the MHLW. The NPO DSRU Japan will be one of the candidates of such bodies. W

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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 exerts the biological activity through its non-genomic action on androgen receptors. Our studies are focused on endocrinological activities of anti-aging herbs which are 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 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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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 and one graduate student is engaged in proteomics work especially on post-translational modification. Adding to them, 6 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 staffs 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

Professor

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Associate Professor

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

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Introduction and Organization

The Department of Clinical Epidemiology and Systems was established in 2007, supported by Banyu pharmaceutical company. Our department took over and enhanced the function and infrastructures of the Clinical Epidemiology Division in the 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 the 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 Pharmacoepidemiology.

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

Teaching activities

The basic lectures of Medical Writing had an enrollment of 114 participants at the clinical auditorium on every Tuesdays (6 series) from September 2 to October 14 in 2008, hosted by the non-profit organization of Japan Medical and Scientific Communicators Association, and under the joint auspices of the three departments of Clinical Epidemiology and Systems, Clinical Trial Data Management, and Ubiquitous Preventive Medicine.

In addition, the public lectures for the trend and future of computerization in clinical trials was held at the Nogizaka school in the international university of health and welfare on November 27, 2008.

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 computer servers in our department and in the Japan Clinical Research Assist Center. In particular, our department was in charge of the secretariat for JCAD study which was comparison of cardiovascular events between combined and normal therapy for patients with coronary narrowing.

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 core member of the quality improvement and assessment committee and chairs of the clinical pathway working group (WG) and the WG for quality care at our university hospital, our department contributes to develop clinical indicators and comparative studies. Since an electronic clinical pathway system was implemented in March, 2008, standardization and improvement of health care are also under way based upon EBM.

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

Associate Professor

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Associate

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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: Ryoza 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.

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) under the Ministry of Economy, Trade and Industry (METI) and an 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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6. Suzuki T: Proteomic analysis of cardiovascular pathologies-From chromatin remodeling to biomarkers-. A research conference of the department of nephrology, the University of Tokyo Hospital. (July 15, 2008, The University of Tokyo Hospital, Tokyo)

Department of Advanced Skin Care (Miss Paris)

Visiting Professor

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Project Research Associate

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Introduction and Organization

The Department of Advanced Skin Care (Miss Paris) is the newest department of the Graduate School of Medicine, established in April 2008. Current member includes 1 visiting professor and 1 project research associate. The supportive department is the Department of Gerontological Nursing/Wound Care Management.

With a rapid extension of the average life expectancy in Japan, many health related problems have occurred. As a consequence of aging, the skin undergoes a number of pathological changes, which lowers the protective mechanism of skin against the adverse effects of mechanical stresses. Eventually, these lead to pressure ulcers, diabetic ulcers or other chronic wounds. Therefore, our goal is to establish "advanced skin care" based on the wellness promotion sciences.

On 29th June, 2008, kick-off meeting of the department of advanced skin care was held. Moreover, the special lecture entitled "Regeneration system of the hair follicle stem cell" presented by Hideo Oshima, MD, PhD, director of plastic surgery, National Hospital Organization Kumamoto Medical Center, was held on 14 November.

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

We focus on the changes of the skin with the aging and its related factors. Based on the information of both healthy people and patients with skin injuries, we try to develop the objective evaluation method of the degree of skin health status. Our study method is ranged from cell biological approaches to clinical epidemiologic approaches. We also make an effort to establish the new translational research in nursing science.

In 2008, the two research projects were started;

- 1) Prevention and management of the metabolic syndrome disease
- 2) Evaluation for the elderly skin and the peristomal skin.

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Department of Chronic Kidney Disease (CKD)

Associate Professor

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Associate

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Homepage

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.
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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 Immunotherapeutics (Medinet)

Project Associate Professor

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Project Research Associate

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Introduction and Organization

The Department of Immunotherapeutics (Medinet) was established on June 1, 2004 as one of the first of 22 departments of the 22nd Century Medical and Research Center in the University of Tokyo Hospital. This Center is a research complex of departments endowed by the Business-Academia partnership. The Department of Immunotherapeutics (Medinet) was contributed by Medinet Co. Ltd., the leading company in this field in Japan. 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.

Research on cancer immunotherapy is directed by Dr. Kazuhiro Kakimi. Dr. Makoto Kurachi who participated in the starting-up period of the department from 2004 to March 2007 as an associate. Dr. Kiminori Kimura joined our team in April, 2007. Our focus remains the study of cancer immunology and promotion of translational research for the development of improved cancer immunotherapy.

When the new building (Central Diagnosis and Treatment Building 2) of the University of Tokyo Hospital became available in July 2006, we moved our department to its 9th floor in September 2006. It is particularly worth noting that the GMP-level Cell Processing Center (CPC) was installed in the department at the same time. A CPC is a critical facility to prepare cells for clinical applications.

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*. 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. We began the outpatient program specializing in cancer immunotherapy in February 2007.

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 system.

In addition to cancer immunology and immunotherapy, our activities include tissue transplantation and transplantation immunology, the development of novel vaccination strategies and identification of unique anti-infectious agents in collaboration with the Department of Cardiothoracic Surgery (Professor Shin-ichi Takamoto).

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:

- 1) Clinical study on safety and efficacy of adoptive transfer of autologous $\gamma\delta$ T lymphocytes in patients with non-small cell lung cancer (IRB approval number 1290).
- 2) A study to evaluate the safety and efficacy of infusions of ex vivo expanded autologous $\gamma\delta$ T cells following zoledronic acid sensitization in patients who received radiotherapy for bone metastases (IRB approval number 1511).
- 3) Clinical trial of the efficacy and safety of autologous $\gamma\delta$ T cell transfer therapy after pulmonary metastasectomy of colorectal cancer (IRB approval

number 1781).

4) Clinical trial to investigate safety and efficacy of the combination of gemcitabine and autologous adoptive $\gamma\delta$ T cell transfer after resection of pancreatic cancer (IRB approval number 1810).

5) A phase I study of vaccination with NY-ESO-1f peptide mixed with OK-432 (Picibanil®) and Montanide® ISA-51 in patients with cancers expressing the NY-ESO-1 antigen (IRB approval number 1935).

Furthermore, we support the following clinical studies in corporation with the Department of Gastroenterology and Hematology, The Tokyo Medical University:

- 1) Clinical trial of intratumoral DC injection after radiofrequency ablation (RFA) therapy for the treatment of hepatitis C virus-related hepatocellular carcinoma (HCC) (C000000451, UMIN00000971).
- 2) Clinical trial of DC therapy for unresectable advanced pancreatic cancer (UMIN000001135).

As part of the above clinical trials, 7 lung cancer, 5 bone metastasis, and 3 metastatic lung tumor patients (15 patients in total) have thus far received infusions of autologous $\gamma\delta$ T cells. The safety and the efficacy of these treatments were evaluated.

Teaching activities

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

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Department of Integrated Molecular Science on Metabolic Diseases

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Homepage

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 DIMSMD 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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Department of Advanced Clinical Science and Therapeutics

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Introduction and Organization

The Department of Advanced Clinical Science and Therapeutics, established at the University of Tokyo in 2004, aims to develop new clinical strategies and therapy in cardiovascular medicine and other areas. This department hopes to develop not only basic research, but also applications to devise new clinical strategies.

Research activities

Followings are our recent basic and clinical research activities.

Basic Research

- New strategies to regulate acute rejection and graft arterial diseases in cardiac transplantation.
- New strategies to regulate acute/chronic myocarditis.
- New strategies to regulate acute myocardial infarction and ischemia/reperfusion injury.
- New strategies to regulate restenosis after coronary angioplasty.
- New strategies to regulate atherosclerosis and aneurism.
- New strategies to regulate systolic/diastolic heart failure.
- New strategies to regulate sleep apnea syndrome and circadian rhythm abnormality.
- New strategies to regulate cardio-kidney syndrome.

- New strategies to regulate oral-pathogen induced cardiovascular diseases.
- Development of gene therapies (anti-inflammation etc.).
- Development of new growth factor treatments (hepatocyte growth factor, etc.).
- Development of new anti-adhesion molecule treatments (anti-inflammation, etc.).
- Development of new anti-extracellular treatments (anti-inflammation, anti-oxidation, etc.).
- Development of new chemical compounds (anti-inflammation, anti-coagulation, etc.).
- Expanding the use of foods and natural extracts.
- Expanding the application of existing drugs and devices.
- Analysis of angiogenesis using in situ hybridization.

Clinical Research

- Gene therapies to prevent restenosis and thrombosis after coronary intervention.
- Pathophysiology of oral disorder and cardiovascular diseases.
- Pathophysiology of sleep apnea syndrome and cardiovascular diseases.
- Pathophysiology of renal dysfunction and cardiovascular diseases.

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Department of Ischemic Circulatory Physiology, KAATSU training

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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 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.

List of papers

Nakajima T, Jo T, Meguro K, Oonuma H, Ma J, Kubota N, Imuta H, Takano H, Iida H, Nagase T, Nagata T. 2008. Effect of dexamethasone on voltage-gated Na⁺ channel in cultured human bronchial smooth muscle cells. *Life Sci.* 82:.

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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. Ryoza Nagai). In January 2008, our new missions have started under the contribution of Theravalues Corporation and Hitachi, Ltd. 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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Research Grant of Takeda Science Foundation(to Morita H)

Research Fund of Mitsukoshi Health and Welfare Foundation(to Morita H)

Young Investigator Imura Award of Japan Vascular Disease Research Foundation(to Morita H)

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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 epidemiological 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/osteoporosis Against Disability) in 2005, 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 on three population-based cohorts with total 3,040 participants in urban, mountainous and seacoast communities of Japan. A second comprehensive clinic visit is scheduled for October 2008 after a follow-up period of 3 years.

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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, and receives funding from Himedic Co. Ltd. and GE Yokogawa Medical Systems, Ltd.

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

Project Associate Professor

Yushi Uetera, Ph.D.

Project Research Associate

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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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Project Research Associate

Shigeyuki Muraki, M.D., Ph.D.

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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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Department of Medical Safety Management

Project Professor

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Shoichi Maeda, Ph.D.

Project Researcher

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Introduction and Organization

The Department of Medical 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 Medical Law Article 21 mandatory reporting to the police. 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 medical treatment lawsuit number has kept increasing according to about twice the ratio for every ten years from about 1970. Though the civil affairs medical treatment lawsuit number shows a plain decreasing tendency in the comparison of years 2004, 2005, and 2006, it is not clear whether this tendency continues.

In our department, while looking straight at the reality of the malpractice and the medical affairs dispute from each aspect of the patient, the medical treatment person, and the society, it aims at a healthy rebuilding of the medical care and the confidence recovery 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 medical treatment person.

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 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.

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Conference Presentations

International Meeting

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Domestic Meetings

Invited Presentation

6. Yasushi Kodama. Exceeding ten years of the medical affairs dispute, from the experience of the Model Project for Investigation and Analysis of Medical Practice Associated Deaths. *Japan Surgical Society 108th Regular Scientific Meeting*. May 16, 2008

Symposium

7. Yasushi Kodama. Ideal way of malpractice investigation as a self-regulation in medical institutions. *Third Scientific Meeting of Japanese Society for Quality and Safety in Healthcare*. November 22, 2008

Lectures

8. Yasushi Kodama. Practices of Dental hygienists. Medical treatment safety management committee and odontology department medical treatment safety task force combination conference. May 28,

- 2008
9. Yasushi Kodama. Looking back on ten years of the medical affairs dispute. Japan Red Cross medical treatment safety promotion department general manager conference. May 30, 2008
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 11. Yasushi Kodama. Case report of therapy cost and compensation money claim event (medical treatment ADR event). Tokyo 3 meeting arbitration business society. July 15, 2008
 12. Yasushi Kodama. Current state of medical affairs dispute, Law and Economics of the compensation amends in view. Medical treatment security policy research conference. September 17, 2008
 13. Yasushi Kodama. Current state and correspondence of medical affairs dispute. Japanese hospital association medical treatment safety manager training course. September 19, 2008
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- investigation for cause of one's death associated with medical practice" (Satoshi Kimura, Principal Investigator), research cooperater
19. Shoichi Maeda. Global COE "Educational research base creation for the next generation life and medical ethics" (Akira Akabayashi, research representative), Person in charge of business promotion
- The Ministry of Health, Labour and Welfare trust business
20. Patient Safety Support Center Comprehensive Support Project
- Lecture meeting and research meeting sponsored by the department
21. Personnel development training seminar for the Model Project of the Investigation of Death Associated with Medical Practice. The University of Tokyo Hospital. March 14-15, 2008

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18. Yasushi Kodama. Public welfare labor science research expense subsidy-medical treatment-general -008 "Research on ideal way of

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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 defective 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 2006. This division consists of the above-mentioned three 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. In 2007, our own achievements have begun to be published.

Teaching activities

In March of 2007 and 2008, total two graduate fellows required for the medical degree. And now a few graduate fellows works 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 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 similar mechanism existed in obese hypertension (1). 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 type of hypertensive disease.

Also, dietary potassium supplementation revealed vascular protection in cuff-induced injury of femoral artery via its antioxidant effect in salt-sensitive hypertension (2), which was the similar to protective action of dietary potassium in cardiac damage in salt-sensitive hypertension. This paper (2) received particular attention, so that a figure of the paper appeared on the cover of the journal "Hypertension". Moreover, we demonstrated that ROS played an important role of the progress of renal and cardiac injury in obese spontaneously hypertensive rats, known as SHR/NDmcr-cps, a model of metabolic

syndrome (3). These results also suggest that aldosterone contributed to reno-cardiovascular damage via ROS overproduction.

In addition, we demonstrated that pepubertal administration of mineralocorticoid receptor blocker suppressed the development of renal injury and hypertension even after its discontinuation in salt-sensitive hypertension model animals and are examining the contribution of its antioxidant effect. This investigation may clarify the pathophysiology of defective lifestyle-induced hypertension and renal damage in pepubertal age.

Clinical investigation: The results of the clinical study were published: L-/N-type calcium channel blocker (CCB) exerted superior antiproteinuric action than L-type CCB, probably due to its sympatholytic effect. The results of the paper had not been presented in Japan before publication. However, after publication, it was featured in the Late Breaking Clinical Trial session of the 51st annual meeting of Japanese Society of Nephrology and the reports about it was published as the topic in "Annual Review Nephrology 2009". We will contribute to another clinical study in future. Now, we are participating in a few clinical studies.

We are investigating a common disease such as hypertension and metabolic syndrome, and can indicate meaningful results.

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7. **Ando K**, Isshiki M, Takahashi K: Effect of combination therapy with telmisartan and low-dose hydrochlorothiazide switching from amlodipine. *Hypertens Res* in press
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Department of Anti-Aging Medicine

Professor

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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, supported by the funds from Coca-Cola Tokyo Research & Development Co. 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), and TRIM44.

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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Department of Clinical Trial Data Management

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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 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.

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Introduction and Organization

Clinical Laboratory Center consists of 11 doctors, a chief technologist, 63 technicians, and 2 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 2008, 232,150 outpatient blood sampling were performed in this section.

The 2nd Section

This section deals with clinical biochemistry and immuno-serology tests. In 2008, over 4,198,907

serum enzyme tests (such as AST and ALT), and 458,071 immunological tests were performed.

The 3rd Section

This section deals with laboratory hematology and DM-related tests, gene analysis tests and urinalysis. In 2008, 978,253 samples were examined for complete blood cell counts, cell surface marker analysis, prothrombin time, fibrinogen, glucose, and HbA1C tests, and 214,281 urine samples were examined.

The 4th Section

This section deals with physiological tests, including circulatory, pulmonary, and neuromuscular function ones. In 2008, 43,640 ECG, 21,277 pulmonary function tests, 19,532 echocardiography tests, 11,721 abdominal echography tests, and 9,823 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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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 8,322 and 9,374 operations, which counts for 1.5 times comparing to those in 2001, were performed in 2006 and 2007, respectively. More recently, the number of operations was 9,868 (1,268

emergency cases) in 2008.

There has been much concern about the apparent increase in the patients who are positive for the microbiological tests such as tuberculosis, MRSA, pseudomonas aeruginosa, HBV, HCV and HIV. Those patients have been increasing by 5-18% per year over the last 4 years. Administrative efforts might be needed more in the near future to protect the staffs as well as the patients against the new infectious agent such as prion.

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 a 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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Department of Clinical Radiology

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Introduction and Organization

In the Department of Clinical Radiology, clinical services on Diagnostic Radiology (imaging and intervention), Radiation Oncology (radiotherapy), Nuclear Medicine and the Radiation Safety Control System are provided in cooperation with radiology technologists and nurses. Present constituent members are as follows: three medical doctors, 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 five 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 two 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. The rate of the non-coplanar radiation therapy is over 25% and surpasses those of other institutions. 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

Professor

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Lecturer

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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 891 in 2008, 797 in 2007.

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 in 2008

[See Department of Perinatal Medicine.]

Rehabilitation Center

Professor

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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 three 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. Fourteen physical therapists and five acupuncture therapists are working in the physical therapy section. In the occupational therapy section, three occupational therapists work for the general rehabilitation service and the other two therapists work for the psychiatric rehabilitation. In the Day-care Unit, a clinical

psychologist and a nurse also work. In 2006, speech therapists and orthoptists who belong to other departments in the University of Tokyo Hospital are going to be included in our department.

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 150 patients corresponding about 15% 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.

- going 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
 - 4) Analysis of motion and energy expenditure in the activities of daily living in the physically disabled
 - 5) Non-invasive evaluation of lower limb motor function in spina bifida
 - 6) Evaluation of higher brain function in patients with spina bifida
 - 7) Disabilities and handicaps in patients with skeletal dysplasias

- 8) Influence of physical therapy to skeletal muscles

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Introduction and Organization

Department of Pathology and Diagnostic Pathology (*) and Division of Diagnostic Pathology of University Hospital have been united to function as a unit. This union is responsible for the pathologic practice of the University Hospital (autopsy and surgical pathology), as well as for education and research of human pathology.

The proper staffs were 1 lecturer, two lecturers (hospital), two associates, and two clinical staffs.

Clinical activities (diagnostic pathology and autopsy)

Annual statistics of the pathologic practice in 2007 fiscal year are 13,090 cases of biopsy, 17,676 of cytology, 658 of frozen histology, 558 of intra-operative cytology and 78 of autopsy (16% as autopsy rate). Clinico-pathological conferences (CPCs) for the two autopsy cases are held every month in the hospital. In 2006, 126th – 136th CPC were held. Furthermore, surgical pathological conferences are regularly held with each clinical division, and discusses the cases of various tumors, including thorax, upper gastrointestinal tract, neurosurgery, liver, pancreato-biliary tract, urology, gynecology, mammary gland, and orthopedics, as well as biopsy

cases of liver, kidney and skin.

Our aim of the pathologic practice is to provide the correct diagnosis as soon as possible. We are addressing 'one-day pathology' using a newly developed rapid-histoprocessing machinery. 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. Lecturer Uozaki is mainly in charge of this project.

We continued to participate the autopsy assessment for "The Model Project for Inspection and Analysis of the Death Associated with Medical Practice" of Health, Labor and Welfare Ministry,.

Teaching activities

The lectures and exercise course of systemic pathology are for the 2nd grade-students. Clinical clerkship and bed-side learning (BSL) course of autopsy and surgical pathology are for the 3rd and 4th grade students, respectively.

The new system of internship has started since 2004, and all interns are required to submit at least one report of CPC case. The Division of Diagnostic Pathology received seven interns in 2007 for the second year program of their internship.

Research activities

We are developing the tumor specific antibodies in collaboration with Genome Science Division, Research Center for Advanced Science and Technology, the University of Tokyo. Based on the DNA array data of various human neoplasms, monoclonal antibodies against candidate gene products are generated. In addition, we are in the process of constructing the tissue array of neoplastic and non-neoplastic tissues in order to facilitate the screening process of immunohistochemistry,.

References

See the corresponding section of Department of Pathology and Diagnostic Pathology

Department of Corneal Transplantation

Associate Professor

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Introduction and Organization

The department of corneal transplantation was established in 1976 as one of clinical sections in the University of Tokyo Hospital. The purpose of the establishment of this section is to carry out and promote corneal transplantation and to perform clinical and basic research in the corneal diseases and corneal transplantation. The section is composed of a director (associate professor).

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

Professor

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Junko Takita, M.D., Ph.D. (Pediatrics/Hematology-Oncology)

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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 of other departments including the department of internal medicine, surgery, gynecology and otorhinolaryngology participate the examinations. The examination rooms moved to the new building in Oct. 2006.

Clinical activities

Endoscopic examinations, including upper gastrointestinal endoscopy, colonoscopy, bronchoscopy, otorhinolaryngological examinations and gynecological examinations, are performed from Monday to Friday. Therapeutic endoscopies, including endoscopic variceal ligation, endoscopic resection including submucosal dissection for esophageal,

gastric and colorectal tumors, and polypectomy for colonic polyps, are recently increasing. 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

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
EGD*	4384	5555	5667	5923	6346	7324	7920	7597	8265	8131	8796	9822
Colonoscopy	1398	2415	2472	2799	3212	3529	3873	3728	4084	4327	4360	4679
Bronchoscopy	190	239	282	233	194	220	207	194	212	201	201	165
EUS**	347	562	569	470	479	583	586	476	461	438	484	402
Laparoscopy	19	7	2	0	-	-	-	-	-	-	-	-
Laryngoscopy	131	96	99	115	154	93	68	61	89	127	91	63
Colposcopy	272	213	153	149	181	103	124	139	88	58	117	256
Total	6741	9087	9244	9689	10566	11852	12778	12195	13199	13282	14043	15387

*Esophagogastroduodenoscopy, **Endoscopic ultrasonography

Research activities

Our researches cover a variety of endoscopic fields in cooperation with other departments.

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Department of Hemodialysis & Apheresis

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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.

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.

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Introduction and Organization

The Clinical Research Center was established in April 2001 as one of the regular departments in the central division in our hospital. The Center not only took over the duties of the former provisional Clinical Trial Research Center, which dealt industry-initiated clinical trials, but also newly-incorporated the commission to support investigator-initiated clinical trials. The staff of the center as of March, 2009, is comprised of one professor, one associate professor, one research associate, seven pharmacists, five nurses, one clinical psychologist and three officials, of which three pharmacist and three nurses were full-time workers with three years' tenure and two officials and one clinical psychologist were part-time workers. The center consists of four subdivisions: Division of consultation on protocol development (one associate professor and one research associate), division of pharmaceutical administration (three pharmacists), division of clinical research coordination (eight nurses, six pharmacists and one clinical psychologist) and division of clerkship (three officials).

Clinical activities

The duties of the center are wide-ranging from serving as a secretariat for the institutional review board (IRB) to supporting the conduct of clinical trials. Clinical trials that we dealt with covered all regulatory

clinical trials for approval and investigator-initiated clinical trials concerned with medicinal treatments.

As an IRB secretariat, to which all the staffs are responsible, we dealt 48 new protocols and 73 ongoing protocols for industry-initiated clinical trials in fiscal 2008. We also dealt with 2 new protocol for investigator-initiated regulatory clinical trials and 57 investigator-initiated non-regulatory clinical trials, which include the ethical use of non-approved drugs. A protocol hearing was held every month for applications of new industry-initiated protocols to facilitate a review with meaningful discussion in the IRB and to give practical advice in carrying out the protocols properly. The meeting was held with the attendance of applicant company representatives, principal and sub investigators and the staffs of the center. We also dealt applications for changes in the initial application documents (594 applications), safety information (747 reports), and other reports in fiscal 2008.

To solve a so-called 'un-approved drugs issue' or 'drug lag issue', participation to global trials was a key issue. For this purpose, University Hospital Clinical Trial Alliance (UHCT Alliance) comprised of 7 national university hospitals (Tokyo University, Niigata University, Gunma University, Shinshu University, Tsukuba University, Tokyo Medical and Dental University and Chiba University) was established in 2006 and is collaborating with each other in continuing improvement of our clinical trial

environments. Until the end of 2008, 37 protocols were introduced to the alliance including 18 multi-national trials.

As for pharmaceutical administration, we took charge of 135 clinical trial drugs and medical devices and filled 1538 prescriptions in fiscal 2008. Pharmacists in the division are also in charge of the primary review of safety information about clinical trial drugs and the database management in the Center. Our databases concerning protocols and subjects were transferred to a new system as a part of the hospital clinical information system in March 2006, allowing the direct access to the clinical trial information from the hospital system.

Clinical research coordinators (CRC) support the implementation of all regulatory clinical trials. The coordination covered all aspects in pursuing clinical trials: preparation for the trials, screening for patients, assistance to obtain patients' informed consent, coordinating outpatients' visit, assistance with inspections, assistance in the preparation of case report forms (CRF), arrangements for monitoring and audits, and arrangements for medical accounting. There were a total of 5172 times of coordination of outpatients' visits and medical treatments of inpatients in fiscal 2008. CRCs also support the implementation of some of the investigator-initiated non-regulatory clinical trials. In 2005, we introduced a principle that beneficiaries should pay for part of a personnel cost of CRCs and adopted three investigator-initiated protocols for the CRC support on this principle.

Publicity activity has been continued including the provision of the information about the protocols under subject recruitment both in our internet home page and in our takeaway leaflets.

The outpatient clinic dedicated for clinical trials moved new building in Nov. 2006 and was newly equipped with consultation counters and a waiting room.

The consultation division started in May 2002 to support the investigator-initiated clinical trial. The mission of the division is to help investigators to conduct clinical research under the ethically and scientifically reviewed protocols. Namely, the division supports protocol development, application to IRB and monitoring of the progress and amendment of clinical trials. As for educational programs of clinical

research for investigators, the division also gives a training course 3 times a year and a symposium every year. The division dealt with 57 new investigator-initiated clinical trials which include the ethical use of non-approved drugs in fiscal 2008.

Teaching activities

The Center accepted 38 fourth grade students for training in collaboration with the Pharmaceutical Department. Arakawa is taking charge of one half-year lecture on clinical pharmacology for the graduate course students in the Faculty of Pharmaceutical Sciences every year. One student belonged to our research labs in fiscal 2008.

The Center is involved as an on-the-job training institution in CRC training programs. In fiscal 2008, we accepted one three-week trainees from the program operated by Pharmacist Training Center.

Research activities

We performed the publication of four original papers written in English, four review papers in Japanese and the 20 presentations in academic conferences in 2008.

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University hospital Medical Information Network (UMIN) Center

Professor

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

Instructor

Hiroshi Nishiuchi, M.S.

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/u hosp/>

- 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

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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Center for Epidemiology and Preventive Medicine

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Associate Professor

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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 four Clinical Divisions (Breast and Endocrine Surgery, Gynecologic Surgery, Ophthalmology and Vision Collection, Oral-Maxillofacial Surgery, Dentistry and Orthodontics).

The staff of the Center for Epidemiology and Preventive Medicine is composed of five physicians (two regular physicians and three 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 four regular nurses and four regular secretaries (from the Medical Affairs Department). 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 nine options: 1) comprehensive cardiovascular examinations, 2) comprehensive cerebrovascular examinations, 3) colorectal cancer screening, 4) uterine cancer screening, 5) breast cancer screening, 6) lung cancer screening, 7) tumor marker diagnosis, 8) estimation of gastric cancer risk, and 9) 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) 2008 from April 1, 2007 to March 31, 2009, the total number of examinees (who had basic examinations and optional examinations) was 4,702, including 1,507 in basic examinations, 410 in complete cardiovascular examinations, 451 in complete cerebrovascular examinations, 252 in colorectal cancer screening, 297 in uterine cancer screening, 341 in breast cancer screening, 458 in lung cancer screening, 491 in tumor marker diagnosis, 357 in estimation of gastric cancer risk, and 121 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 2008, we issued 758 letters of referral to other departments in our hospital and 44 to other hospitals.

We have expanded our public relations efforts and during the FY 2008 our brochure has reached its ninth edition and 20,000 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. The Center for Epidemiology and Preventive Medicine has attracted much media attention and was covered by the press including the well-known magazine, *ATES*.

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- (3) Suzuki T: Molecular markers for cardiovascular biomarkers to proteomic discovery. Meet The Specialist 2008 (August 22, 2008, The University of Tokyo Hospital, Tokyo)
- (4) Suzuki T: Proteomic analysis of cardiovascular pathologies-From chromatin remodeling to biomarkers-. A research conference of the department of nephrology, the University of Tokyo Hospital. (July 15, 2008, The University of Tokyo Hospital, Tokyo)

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 Regenerativen 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 Regenerativen 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 nano-micelle technology and to generate, to devise methods to precisely control 3D shape of biomaterials, and to transplant regenerated bone and cartilage. To achieve these goals, we are conducting research on bone and cartilage biology, developmental biology, stem cell biology and regenerative medicine.

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.

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. 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 three 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.

- Launched the “22nd Century Medical Center”
- Launched the new central hospital building
- Enhanced functions in the inpatient ward (expansion of ICU/CCU, increase in number of beds in the Psychiatry Department and GCU)

- Reduced the average length of hospital stays, and improved the bed occupancy rate
- Achieved reductions in drug costs and costs for medical materials

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. The division is also conducting research into the development of an education program for healthcare management, and educates students working in health sector since 2007.

(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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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. The 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 complements the Clinical Education Center by providing fieldwork for clinical training. It also offers clinical services to patients with various development problems and places an emphasis on research to provide evidence-based clinical and educational activities.

Clinical activities

In the year 2008, the Department of Child Psychiatry consisted of 8 psychiatrists including 3 full-time child psychiatrists and 8 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 Pervasive Developmental Disorders (PDD), Attention-Deficit/Hyperactivity Disorder (AD/HD), Learning Disabilities (LD), Mental Retardation (MR), tic disorders and child Obsessive-Compulsive Disorders (OCD).

The number of new patients in the year 2008 was more than 500, in contrast to 300 in the year of 2005. This indicates an increase of about 70% compared with that of the year of 2005. Among the new patients, about 50% were patients with disorders of psychological development including LD, with PDD being the most prevalent diagnosis. The second most prevalent diagnosis was tic disorders (11%), followed by AD/HD (11%) and stress-related disorders (9%). The age group of these patients was distributed widely from early infancy to adulthood, and the largest number of patients being those in the late infancy to early childhood group.

The number of follow-up patients has been increasing consistently and become 2.3 times of that in the year of 2005. Among follow-up patients, disorders of psychological development were again the most prevalent at about 50%, followed by tic disorders, stress-related disorders, AD/HD and mood disorders. About half of the patients at follow-up were adult patients, especially high in number were patients in their twenties, constituting a total of 20%. This highlights the need for long-term follow-up in patients with developmental disabilities.

Clinical activities are largely divided into two areas of general child psychiatry outpatient services and interventions for children 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 children consist of "developmental psychology outpatient services" and "short-term group therapy". Patients involved in interventions are children with developmental disabilities, and individualized cognitive developmental therapy is planned for each child. "Developmental psychology outpatient clinic" provides services in the following areas: (1) evaluation of cognitive and behavioral development, (2) individual treatment of the child (3) counseling of parents and providing information to the child's support network (relatives, schools). "Short-term group therapy" is a 10 session group therapy for a small group of children with similar developmental levels. These services are provided mainly by psychologists under the supervision of child psychiatrists.

Education

As part of the Clinical Education Center of Mental Development, two training courses (Course A and B) are offered for graduate level students and various mental health professionals including psychiatrists and pediatricians. Course A is a lecture course which incorporates an interactive component with role-play exercises and case conferences. Course B is an

intensive training course, which includes more clinical experience through participation in intervention and psychological assessment.

Course A is composed of 11 sessions of 3 hour lectures and is offered twice a year, with a total of approximately 100 trainees per year. Trainees consisted of a wide range of professionals, including those in the medical field, such as physicians, psychologists, educators and social workers. This mixture of a variety of professions laid the groundwork for creating a multidisciplinary network for professionals involved in issues related to mental development. Feedback from questionnaires indicated that 80% of the trainees found the course useful.

Course B is offered for a duration of 6 months, with 3 days per week of clinical training. Trainees have included a pediatrician, a psychiatrist, a speech therapist, and a psychologist.

A seminar and symposium is held annually in order to facilitate understanding of mental development and developmental disorders among the general public. In the year 2008, a seminar entitled "Facilitating social participation of adolescents with developmental disorders" and a symposium entitled "Understanding and support for developmental disorders -from the view point of life-span development" each attracted an audience of about 200 and 700 people respectively.

Undergraduates and psychiatry residents from the University of Tokyo have opportunities to observe evaluations and outpatients services as part of their course. They are also required to actively participate in "short-term group therapy".

Research

We participate in investigation of etiology and development of effective treatment on PDD and AD/HD, 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 PDD 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 OCD are being evaluated.

Neuropsychological research

Neuropsychological data on PDD, AD/HD 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 PDD 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 endocrinologic change including thyroid hormone in PDD. In addition to the molecular genetic study, investigation of specific family and environment of Tourette syndrome is being undertaken.

Neuroimaging

Studies include structural MRI, MEG and Near-Infrared Spectroscopy (NIRS) and exploration of the pathogenesis of developmental disorders such as PDD. The main focus is the examination of prefrontal blood flow in PDD and Tourette syndrome by NIRS which is non invasive and easily applicable to children and developmentally disabled individuals.

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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 2008.

The cumulative number of patients who consulted our palliative care team was over 1300 (20.3 average daily patients). The maximum monthly patients were 58 of December (28.9 daily patients). According to site of the cancer, 402 cancers were divided into 49 pancreas, 36 uterine, 32 lungs and so on. We visited almost all the ward in the hospital. According to gender, a total of 402 patients were divided into 219 males and 183 females. According to the age group, there were 140, 103, and 81 in sixties, seventies, and 50 years old, respectively. 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 20 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.
 - pain control
 - delirium control
 - Introduction of the guideline and its use
 - Basic drug therapy for palliative care
 - 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, Chinese medicine specialist, 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

Director & Professor

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

Vice-director & Lecturer

Jun Goto, M.D., Ph.D.

Homepage

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 Monday every month.

Counseling of participants in researches including genome or gene analysis is a duty with which the hospital and the faculty charge the department.

To build suitable clinical systems including modern genomic medicine we are cooperating with other departments. We are participating in Marfan's Syndrome Clinic which is managed collaboratively by

the Departments of Cardiovascular Surgery, Cardiovascular Medicine, Pediatrics, Spinal Surgery and Ophthalmology.

In collaboration with Clinical Laboratory Center, Pharmaceutical Services, Departments of Planning Information and Management, and several clinical departments we started pharmacogenetics tests in 2006. Those include tests for proton inhibitor, warfarin, irinotecan, and tacrolimus.

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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.

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 Mitsuishi

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 Biomechanical 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.

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 Quantum Engineering and System Science, School of Engineering

Department of Nuclear Engineering and Management, School of Engineering

Research Center for Advanced Science & Technology 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 elucidate mechanisms and to establish cures of arteriosclerosis

Laboratory of Artificial Organs

Division of Artificial Organs & Transplantation: Katsutoshi Naruse and Lei Guo

Institute of Industrial Science and Center for Disease Biology and Integrative Medicine, Graduate School of Medicine: Yasuyuki Sakai

Laboratory of Artificial Organs consists of researchers belonging to Division of Artificial Organs & Transplantation, and Sakai Laboratory. We have been collaborating in the research of bioartificial liver support systems in the past 10 years. Our current specialization is, development of artificial liver support, clinical use of new apheresis therapy, development of transgenic pig producing human serum albumin, and development of implantable liver tissue equivalents.

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 Engineerin, 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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University Hospital

Pharmaceutical Service

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Introduction and Organization

We have 9 faculty members, 52 pharmacy staffs, 32 pharmacy residents, and 14 graduate students and 5 undergraduate students from the faculty of pharmaceutical sciences (as of December 1st, 2008). In addition, project associate professor (Akihiro Hisaka, 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. 2,260 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 2008)

Number of items on in-hospital formulary:	2,260
Number of prescriptions (ps.) filled or preparation (pp.) (annual)	
out-patients :	475,890 ps.
(outside :	406,171 ps.)
(inside :	69,719 ps.)
Out-patient chemotherapy:	6,786 ps.
in-patients :	213,518 ps.
injection drugs :	189,552 ps.
IVH :	16,686 pp.
chemotherapy :	12,570 pp.
TDM consultations (annual) :	15,660
Numbers of hospital pharmaceutical cares (annual):	3,730

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 pharmaceutics and practical knowledge of prescription and risk management to them. For the students in the health sciences and nursing, we are in charge of clinical pharmacokinetics lectures as a part of a compulsory subject, "Pharmacology and Toxicology".

For students in the faculty of pharmacy, we are in charge of 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 "Advanced Course of Medical Pharmacy"

(every other year) as a cooperator of the Clinical Pharmacokinetic. 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. We are responsible for the hospital practice courses (10 days in total) and teach practical techniques of pharmacists such as drug preparations and patient consultation. In addition to these, we educate 4th year students and graduate students who moved to the Clinical Pharmacokinetics.

In 2008, 32 pharmacists completed our one-year post-graduate training course. They learned various practical knowledge and techniques necessary for hospital pharmacists. This course takes a role of 6-years education of the faculty of pharmacy in advance which will start in 2009. In addition, we are promoting life-long education of pharmacists in the local area by holding monthly regular technical workshop.

Research activities

A proper medication requires scientific evidences. However, it is not fully understood that what the target for main and side-effect of the drug is, as well as the enzymes and transporters involved in the disposition of drugs. Moreover, a number of patients are waiting for development of new pharmacotherapy. We are trying to clarify basic mechanisms of the genetic or acquired diseases to develop useful pharmacotherapy for an individual patient. Our research fields include the regulation of the expression and function of transporters related to the pharmacotherapy, polymorphism of drug metabolizing enzymes and transporters governing the drug disposition, and drug information research.

Followings are the topics of our recent research:

- 1) Regulation of transcription and function of transporters in the liver and intestine involved in cholesterol homeostasis.
- 2) Basic and clinical approach to prevent and cure drug induced liver injury.
- 3) Intracellular trafficking and dynamic rearrangement of transporter complexes.
- 4) Regulation of intracellular trafficking and transcription of signaling molecules involved in bone homeostasis
- 5) Polymorphism of drug metabolizing enzymes and transporters. Quantitative prediction of clinical effects.
- 6) Clinical data analysis and utilization of drug package insert, information on drug-drug interaction, and patient data for the development of safer and better medications for patients.

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**Center for Disease Biology and
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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 definitively contribute to the direct therapeutic application of our findings. Since our rationale is to challenge to uncharacterized disease mechanisms and physiologies, we will not restrict our interest, strategy or technique employed, in certain specific field. Rather, we will expand our research area by establishing different collaborations with a broad spectrum of 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 at that time, 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. Our laboratory belongs to the Section of Functional Biology in the Graduate School of Medicine. The name of our laboratory has been changed from Division of Biophysics to Laboratory of Structural Physiology in the April, 2008.

Teaching activities

In 2008, we were involved in undergraduate education of Physiology. Particularly, we taught endocrine physiology and was responsible for student experiments. We have four graduate students in our own laboratory.

Research activities

Functional imaging is a central theme in modern biology and medicine. All biological functions involve a multitude of interactions at the molecular, cellular, and system levels, and it is ultimately desirable to perform molecular and cellular imaging in intact preparations in which the original *in vivo* functions are preserved. We have been exploring two-photon excitation microscopy with a new type of laser, an infrared femtosecond-pulse laser, as a means to achieve this goal. The two-photon microscope has the ability to penetrate deep into tissues and is the only imaging instrument that allows investigations of intact tissues at the cellular and molecular levels. Two-photon microscopy can also be readily combined with molecular biological and other physiological methods, and it promises to provide important insight into various biological processes in the coming years. Our research interests have two main focuses: (1) the dynamics of synapses in the cerebral cortex and (2) exocytosis in both neurons and secretory cells. We welcome multidisciplinary collaborations to promote our research goals and to help to adapt the new microscopic techniques and lasers to a wide range of

biomedical applications.

1) The subspine organization of actin fibers regulates the structure and plasticity of dendritic spines.

Synapse function and plasticity depend on the physical structure of dendritic spines as determined by the actin cytoskeleton. We have investigated the organization of filamentous (F-) actin within individual spines on CA1 pyramidal neurons in slices of rat hippocampus. Using two-photon photoactivation of green fluorescent protein fused to β -actin, we found that a dynamic pool of F-actin at the tip of the spine quickly treadmilled to generate an expansive force. The size of a stable F-actin pool at the base of the spine depended on spine volume. Repeated two-photon uncaging of glutamate formed a third pool of F-actin and enlarged the spine. Creation of this "enlargement pool" required calmodulin. The spine often released the enlargement pool into the dendritic shaft, but the pool had to be physically confined by a spine neck for the enlargement to be long-lasting. Ca^{2+} /calmodulin-dependent protein kinase II regulated this confinement. Thus, we have revealed that spines have a mechanical nature that is regulated by the three pools of F-actin (Ref. 1).

2) Protein-Synthesis and Neurotrophin Dependent Structural Plasticity of Single Dendritic Spines

Long-term potentiation (LTP) at glutamatergic synapses is considered to underlie learning and memory, and is associated with enlargement of dendritic spines. Because consolidation of memory and LTP requires protein synthesis, it is important to clarify how protein synthesis affects spine enlargement. Repetitive pairing of postsynaptic spikes and two-photon uncaging of glutamate at single spines (spike-timing protocol) displayed both immediate and gradual phases of spine enlargement in CA1 pyramidal neurons. The gradual enlargement was strongly dependent on protein-synthesis and BDNF action, often associated with spine twitching, and was induced specifically at the spines which were immediately enlarged by the synaptic stimulation. Thus, spike-timing protocol is an efficient trigger for BDNF secretion, and induces protein-synthesis dependent long-term enlargement at the level of single spines (Ref. 2).

3) Principles of Long-Term Dynamics of Dendritic Spines

Long-term potentiation (LTP) of synapse strength requires enlargement of dendritic spines on cerebral pyramidal neurons. Long-term depression (LTD) is linked to spine shrinkage. Indeed, spines are dynamic structures: they form, change their shapes and volumes or can disappear in the space of hours. Do all such changes result from synaptic activity, or do some changes result from intrinsic processes? How do enlargement and shrinkage of spines relate to elimination and generation of spines, and how do these processes contribute to the stationary distribution of spine volumes? To answer these questions, we recorded the volumes of many individual spines daily for several days using two-photon imaging of CA1 pyramidal neurons in cultured slices of rat hippocampus between postnatal day 17 to 23. With normal synaptic transmission, spines often changed volume or were created or eliminated, thereby showing activity-dependent plasticity. However, we found that spines changed volume even after we blocked synaptic activity, reflecting a native instability of these small structures over the long term. Such "intrinsic fluctuations" showed unique dependence on spine volume. A mathematical model constructed from these data and the theory of random fluctuations explains population behaviors of spines, such as rates of elimination and generation, stationary distribution of volumes and the long-term persistence of large spines. Our study finds that generation and elimination of spines are more prevalent than previously believed, and spine volume shows significant correlation with its age and life expectancy. The population dynamics of spines also predict key psychological features of memory (Ref. 3).

4) Three-dimensional mapping of unitary synaptic connections by twophoton macro photolysis of caged glutamate.

To understand the precise microarchitecture of the cortical circuitry, it is crucial to know the distribution of synaptic connections and their synaptic strengths at the level of a single cell, rather than a group of cells. Here, we describe a new application of two-photon photolysis of caged glutamate that enabled us to induce an action potential in only a small number (~5) of pyramidal neurons by increasing the volume of

two-photon excitation by reducing the effective numerical aperture of the objective. We performed whole-cell patch-clamp recordings from layer 2/3 pyramidal neurons in the rat visual cortex and stimulated many neurons in a large three-dimensional space (~600 x 600 x 100µm) including neurons in layers 2/3 and 4 using this new technique. We mapped the density and amplitude of unitary excitatory postsynaptic currents and found that the basic microarchitecture of excitatory synaptic connections consists of two regions: a columnar, dense core region with a radius of 150 µm and an outer, sparse region. The dense core region includes the majority of strong synaptic connections in layer 2/3. Our results reveal the columnar organization of synaptic connectivity in the rat visual cortex, where functional columns have not been clearly demonstrated. Thus, this technique will be a uniquely powerful tool for quantifying synaptic connectivity and manipulating neural activity at the single-cell level (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. Sakai 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. Sakai 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
- Application of the smart biomaterials for drug delivery

3) Process design of tissue regeneration

- Mathematical understanding and process design of tissue regeneration *in vitro* and *in vivo*, especially in peritoneum

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Laboratory of Clinical Biotechnology

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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, which is one of major goals for Research Cluster for Frontier Medicine Development at The University of Tokyo Hospital and The Center for NanoBio Integration (CNBI) at The University of Tokyo. 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 Nano-Bioengineering Education Program (NBEP) and Global COE (GCOE) program, which started in 2004 and 2008, respectively, 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 lecturer and several project staff members belonging to the CNBI, NBEP and GCOE.

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 diagnostic 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) and cisplatin (CDDP) 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, and comprises of Professor, Associate Professor, and Assistant Professor and other staff members as well as postdoctoral fellows, graduate and undergraduate students. The laboratory settings have been renovated, which makes it possible to start research and educational activities in full capacity as of January, 2006. Staff members have been engaged in environmental toxicology for many years at the National Institute for Environmental Studies, Tsukuba, and the mission of this division for research and education is described below.

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 vi vo* and to establish *in vi tro* 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

Laboratory of Animal Resources (Section of Animal Research) was established as Animal Center for Biomedical Research in April 1971 to provide laboratory animal husbandry and veterinary consultation services for the investigators in the Faculty of Medicine. The first full-time teaching staff, a veterinarian, was employed in April 1972. The building was completed in March 1973, and the center began to provide services for animal experimentation in April 1973. Animal Center for Biomedical Research was at first a facility attached to the faculty. In 2003, it was reorganized as the Section and Animal Research belonging to the Center for Disease Biology and Integrative Medicine (CDBIM). In 2008, the Laboratory of Animal Resources was established as a research laboratory, standing side by side with the section.

The members of this laboratory (including section) are 2 teaching staffs, 2 technical support staffs, the assistant manager of CDBIM, a teaching assistant, 3 assistant laboratory animal technicians, and 4 assistance clerks. In addition, about 10 contracted employees work together with us in the building to maintain the facilities; animal care, air-conditioning, cage-washing, etc.

The laboratory animals breeding in the building are macaque monkeys, dogs, swine, rabbits, guinea pigs, rats, mice, and chickens. All investigators in the University of Tokyo are able to use facilities in our building after the registration. The number of registered persons was 257 at the end of 2008

academic year. The most of them were the investigators in the Graduate School of Medicine.

Supporting activities

One of our missions is to provide quality care for all animals breeding in our building. The other is to assist the registered patrons in their mission of quality research with respect to the use of laboratory animals. In particular, teaching staffs have overall responsibility for the health and welfare of animals used in research. The office of this 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). We check submitted animal experiment plans to the committee whether the plans would be carried out in consideration of animal welfare, and then give comment and/or advice to respective principal investigators. The committee (Chair, Prof. Hiroki Kurihara) will review the latest plans and will approve, withhold approval, or require modifications to secure approval in accordance with law, regulations and University policies governing the use of animals.

Teaching activities

Our teaching responsibility is to give lectures on Laboratory Animal Science to the 2nd-year students (M0) at the School of Medicine. The teaching staff lectured on the following subjects.

- (i) Animal Welfare, Law, Rules and Regulations
- (ii) Refinement of Animal Experiments (Anesthesia

and Euthanasia)

- (iii) Animal Breeding and Animals Used in Medical Science
- (iv) Infectious Diseases of Laboratory Animals and Zoonoses

The teaching staff gave lectures to the laboratory animal managers, researchers and animal technicians at the Graduate School of Medicine on the following contents.

- (i) Items related to pertinent laws and ordinances, bylaws, guidelines
- (ii) Items related to animal experiments and the handling of laboratory animals
- (iii) Items related to the care and management of laboratory animals
- (iv) The elements of Laboratory Animal Science

Research activities

Each research associate has own research themes, and they are responsible for the research in this section. Followings are the research profiles.

- 1) Development of reproductive engineering techniques for application to epigenetics research and conservation of research bioresources: Reproductive engineering techniques in mammals have been extensively used for research, clinical, and industrial purposes. Our aim is to develop reproductive engineering techniques that can be applied to epigenetic researches and conservation of genetic bioresources, especially laboratory mice. Those techniques include nuclear transfer, microinsemination (ICSI), and embryo/gamete cryopreservation and we hope that these would unravel a mystery of germ cells and totipotency.
- 2) Development of new stem cell lines as experimental models for reproductive biology and regenerative medicine: Stem cells are populations of cells with the potential of self-renew and differentiation. We have been developing new stem cell lines including mouse and rabbit ES cells and mouse thecal stem cells. They provide us with invaluable experimental models for reproductive biology and regenerative medicine.
- 3) Development of immunoassays based on nucleic acid amplification technology: Rapid and ultra-sensitive techniques to detect a trace amount of

pathogen in blood, feces, and water are very important for both human and animal healthcare. We have been developing new immunoassays based on nucleic acid amplification technology (NAT). We have also been developing new immunohistochemical diagnoses based on NAT.

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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.

Rad51B dysfunction due to chromosomal translocations has been found in some benign tumors, particularly in uterine leiomyomas. In Rad51B mutant cells, the Rad51-dependent recombinational repair pathway is impaired. In addition, centrosome aberrations and aneuploidy were found to be increased in these cells. Haploinsufficiency of the gene causes these aberrations. Thus, Rad51B plays a role in centrosome and chromosome integrity.

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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Office of International Academic Affairs

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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 2008 (April through March).

1. International Educational Exchange

1.1 Student counseling about education and research

In 2008, there were 154 foreign students (38 countries) officially registered in the Graduate School of Medicine. Many inquiries were received during this period from prospective applicants for foreign student and trainee status: responses were sent to 81 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 65 people attended in 2008, 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 2008 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, nine University of Tokyo students have taken research electives at the University of Pennsylvania every year, and one student from the University of

Pennsylvania has taken a clinical elective 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, fourteen University of Tokyo students visited to attend clinical electives at Johns Hopkins University, and four student 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, five University of Tokyo students have attended clinical electives at the University of Michigan Medical School, and two 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, four University of Tokyo students visited to attend research electives at Munich University, and two 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, five 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 four 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 five 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 30 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. International contacts in research and scientific fields

2.1 Promotion of academic exchange between Japan and Thailand

Through the good offices of the Japan Society for the Promotion of Science, a 10-year program of scientific exchange with Mahidol University in Thailand began in 1999. Quite unlike previous forms of academic exchange, this one is designed from the start to achieve results by focusing clearly on one area of research and on specific outcomes. The focus is on infectious diseases and related fields, within which research projects are underway in HIV, in new and re-emerging infections, and in other related areas. A total of 18 researchers were invited to Japan (683 researcher-days) and 9 Japanese researchers were sent abroad (70 researcher-days) in 2008.

3. 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 2007, eight young researchers from the Graduate School of Medicine at the University of Tokyo began studying at the partner institutions in the USA.

4. Education and research

3.1 Education

In 2007, Dr. Joseph Green and Dr. Toshiyuki Maruyama taught a course open to all students in the Graduate School of Medicine: Introduction to Clinical Epidemiology Research.

In 2007, 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 2007, 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

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Headache, Mental Health, and Use of Medical Resources: Health Diary Study in Japan. *J Health Sci*, 54(1), 30-36, 2008.

The International Research Center for Medical Education (IRCME)

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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.

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 not only in Japan but also other foreign countries. Compared with other Western distinguished universities, however, activities and research in international cooperation area have been weak. The strength of IRCME is to implement educational cooperation projects in health area supported by official development assistance. Such an approach takes longer time but will influence people in developing countries with sustainability and independence.

To fulfill the mission, faculty and staff in IRCME conduct research on a wide range of topics in undergraduate and postgraduate medical education. One of our objectives is to establish a new methodology of effective and efficient implementation of medical education reform by the information obtained from the practice of international cooperation in medical education.

IRCME also makes important contributions to undergraduate and postgraduate medical curricula of

the Faculty of Medicine to raise awareness of international cooperation and help Japanese medical practitioners develop interest in international activities.

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 (Jul 2008- Jun 2011). Counterpart of the project has been Ministry of Higher Education and Kabul Medical University.
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)

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 2008, we accepted four visiting professors:

- Dr. Shirin Aqa Zarif (1 Feb-14 Mar 2008, Vice Chancellor, Kabul Medical University, Afghanistan)
- Dr. Mohammad Farid Barnayar (1 Feb-14 Mar 2008, Vice Chancellor, Kabul Medical University, Afghanistan)
- Dr. Dwi Tyastuti Kusuma (1 Mar-30 Apr 2008, Lecturer, Family Medicine, Islamic University, Indonesia)
- Dr. Michael F. Lubin (7 July-6 November, Professor, General Internal Medicine, Emory University, USA)

They offered several seminars, lectures for international trainees, and many suggestions to IRCME.

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