

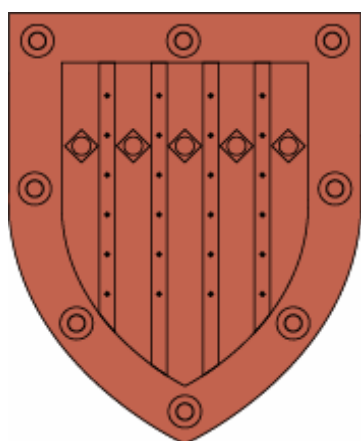
東京医学

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ANNUAL REPORT OF
THE GRADUATE SCHOOL OF MEDICINE
AND
THE FACULTY OF MEDICINE
THE UNIVERSITY OF TOKYO
REPORTS FOR THE PERIOD April 2004 March 2006



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THE UNIVERSITY OF TOKYO FACULTY OF MEDICINE

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東京医学
Tokyo J. Med. Sci.

ANNUAL REPORT OF THE GRADUATE SCHOOL OF
MEDICINE

THE FACULTY OF MEDICINE
THE UNIVERSITY OF TOKYO

REPORTS FOR THE PERIOD April 2004-March 2006

Introduction

This is the report of the University of Tokyo's Faculty of Medicine and Graduate School of Medicine for the years 2004 and 2005. Here we document each department's research and educational activities.

The University of Tokyo has an 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.

Throughout 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.

Nobutaka Hirokawa

Dean, Faculty of Medicine and Graduate School of Medicine

The University of Tokyo

March, 2006

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Artificial Organ and Transplantation Surgery	
(See Department of Artificial Organ and Transplantation Surgery)	
Cardiovascular Surgery (See Department of Cardiothoracic Surgery)	
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Anesthesiology and Pain Relief Center (See Department of Anesthesiology)	
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Ophthalmology and Vision Collection (See Department of Ophthalmology)	

Orthopaedic Surgery and Spinal Surgery (See Department of Orthopaedic Surgery)	
Otorhinolaryngology, and Auditory and Voices Surgery (See Department of Otorhinolaryngology and Head & Neck Surgery)	
Rehabilitation Medicine (See Department of Rehabilitation Medicine)	
Plastic, Reconstructive and Aesthetic Surgery (See Department of Plastic and Reconstructive Surgery)	
Oral-Maxillofacial Surgery Dentistry and Orhtodontics (See Department of Oral-Maxillofacial Surgery)	
Pediatrics (See Department of Pediatrics, Department of Developmental Pediatrics)	
Pediatrics Surgery (See Department of Pediatrics Surgery)	
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編集後記

Teaching, Research, Secretarial and Administrative Staffs

Chief Members of Administration

Dean, Graduate School of Medicine (Dean, Faculty of Medicine)		Nobutaka Hirokawa
Chairman, School of Health Sciences and Nursing		Kai Ichiro
Director, Medical Library		Ouchi Yasuyoshi
Director General, University Hospital		Ryozo Nagai
Director, Center for Disease Biology and Integrative Medicine		Takao Shimizu
The director of the International Research Center for Medical Education.		Kimitaka Kaga

Graduate School of Medicine

Molecular Cell Biology

Department of Cell Biology and Anatomy	professor	Nobutaka Hirokawa
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	Tomoyuki Takahashi
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
	professor	Shogo Ueno

Neuroscience

Department of Basic Neuroscience	professor	Yasuo Ihara
Department of Speech and Cognitive Sciences		
Department of Clinical Neuroscience	professor	Nobumasa Kato
	professor	Shoji Tsuji

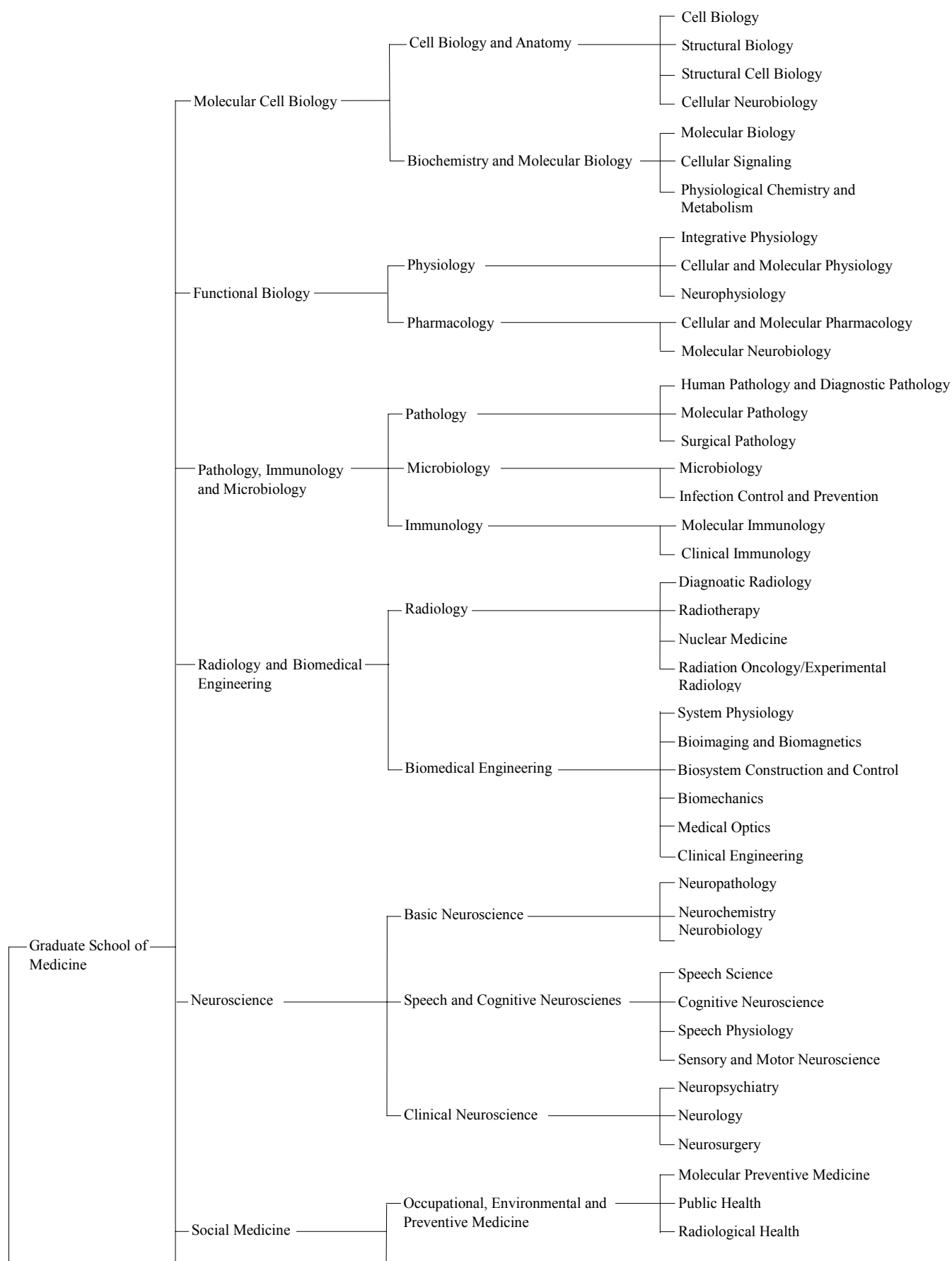
	professor	Norito Saito
Social Medicine		
Department of Occupational, Environmental and Preventive Medicine	professor	Koji Matsushima
	professor	Yasuki Kobayashi
Department of Forensic Medicine, and Medical Informatics and Economics	professor	Kenichi Yoshida
	professor	Kazuhiko Ohe
Internal Medicine		
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
	professor	Osamu Tsutsumi
Department of Pediatric Science	professor	Takashi Igarashi
	professor	Kouhei Hashizume
Department of Aging Science	professor	Yasuyoshi Ouchi
Surgical Sciences		
Department of Surgery	professor	Shinichi Takamoto
	professor	Michio Kaminishi
	professor	Masatoshi Makuuchi
	professor	Tadaichi Kitamura
	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	Kimitaka Kaga
Department of Vital Care Medicine		
	professor	Naoki Yahagi
Health Sciences and Nursing		
Department of Health Sciences	professor	Yasuo Ohashi
	professor	Ichiro Kai

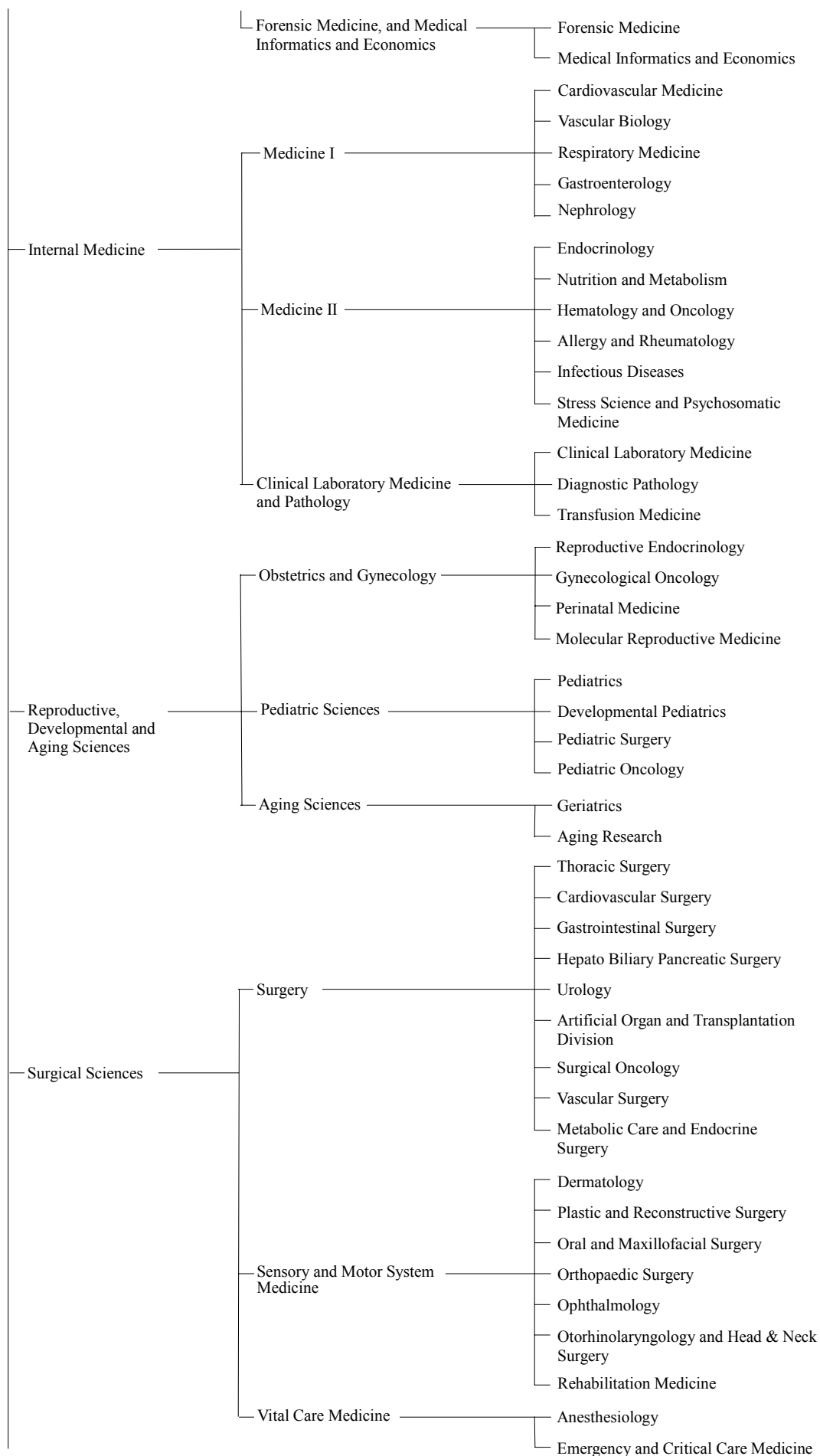
Department of Nursing Sciences	professor	Akira Akabayashi
	professor	Katsuya Kanda
	professor	Keiko Kazuma
	professor	Sachiyo Murashima
	professor	Hiromi Sanada
International Health		
Department of International Social Medicine	professor	Susumu Wakai
Department of International Biomedical Sciences	professor	Katsushi Tokunaga
	professor	Hiroshi Ushijima
	professor	Chiho Watanabe
	professor	Kiyoshi Kita
	professor	Kazuhiko Yamamoto
International Academic Affairs		
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 (Amniotec Inc.)		
	Associate professor	Satoru Yamagami
Department of Clinical Vascular Regeneration(Daiichi Pharmaceutical Co.)		
	Associate professor	Hiroyuki Koyama
Department of Bone & Cartilage Regenerative Medicine		
	Associate professor	Chung, Ung-il
Department of Hematopoietic Regeneration	Associate professor	Seishi Ogawa
Department of “Menicon” Cartilage of Bone Regeneration		
	Associate professor	Kazuto Hoshi
Department of Clinical Renal Regeneration		
	Associate professor	Keiichi Hishikawa
Department of Developmental and Medical Technology(Sankyo)		
	professor	Hiroshi Suzuki
Department of Metabolome	professor	Ryo Taguchi
	Associate professor	Yoshiya Oda
Department of Systematic Clinical Oncology	Associate professor	Shin Sasaki
Hospital Logistics by Sagawa Express Co.,Ltd.	professor	Hirohito Kuse
Clinical Molecular Epidemiology(Tanabe Seiyaku Co., Ltd.)		
	Associate professor	Takanari Gotoba
Immunotherapeutics (Medinet)	Associate professor	Kazuhiro Kakimi
Healthcare Related Informatics (NTT DATA CORPORATION)		
	Associate professor	Shinya Oku
Division of Total Renal Care Medicine	Associate professor	Shinya Kaname
Integrated Molecular Science on Metabolic Diseases		
	Associate professor	Toshimasa Yamauti

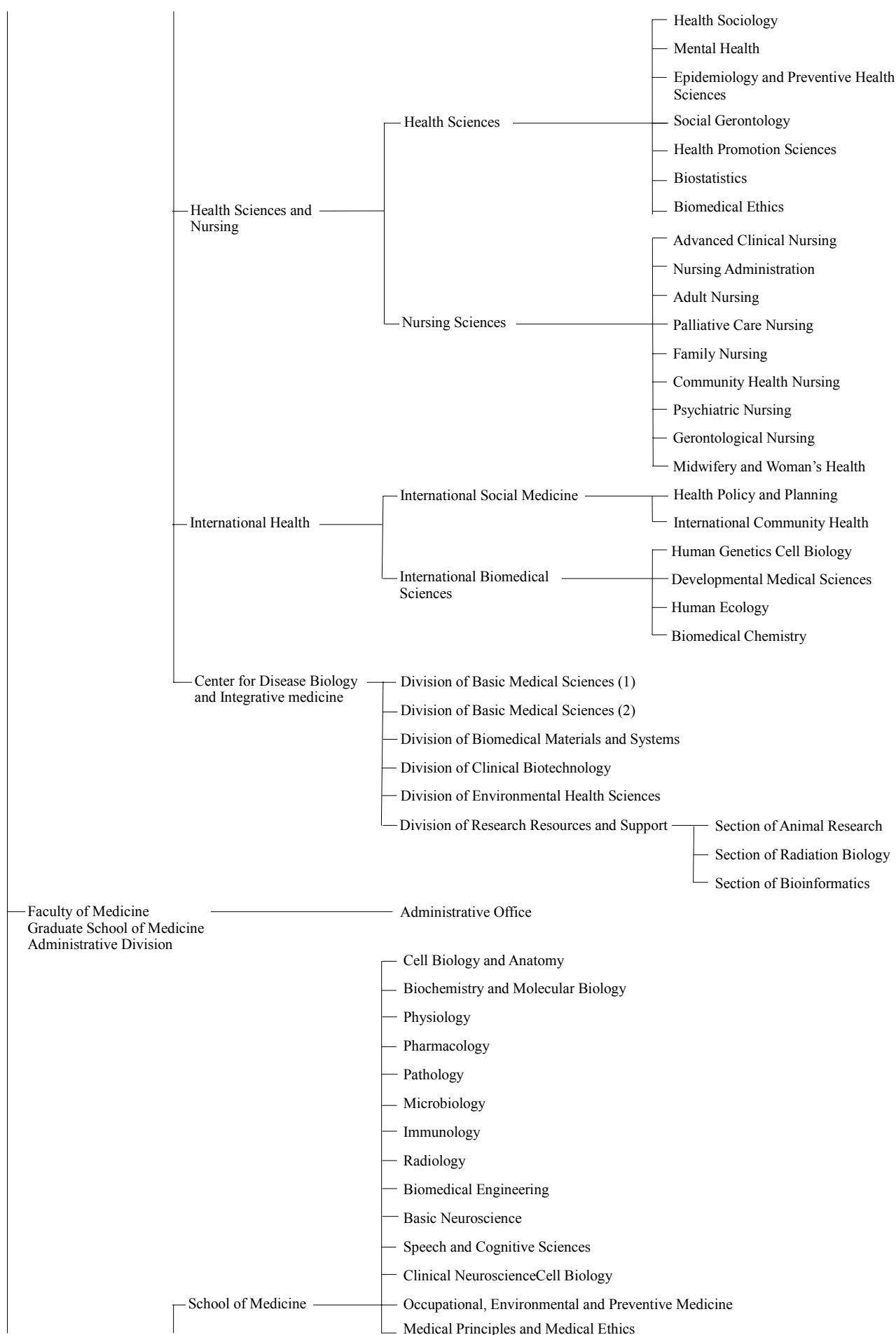
Department of Advanced Clinical Science and Therapeutics	Associate professor	Koji Kawakami, Masataka Sata
Sato Sports Plaza Co., Ltd Kaatsu Training	Associate professor	Toshiaki Nakajima
Department of Sleep Disorder Research(Alfresa)	Associate professor	Takashi Ebisawa
Translational Research Based on the Clinical Database	Associate professor	Dobun Hayashi
Department of Joint Disease Research	Associate professor	Noriko Yoshimura
Health Care Management and Policy	professor	Hideki Hashimoto
Computational Diagnostic Radiology and Preventive Medicine	Associate professor	Naoto Hayashi
Helth Service Center	Associate professor	Hoshio Uehara, Tsukasa Sasaki, Yasushi Okubo
International Research Center for Medical Education Director Kimitaka Kaga		
professor Kiyoshi Kitamura	Associate professor	Junji Ohtaki
University Hospital		
Clinical Divisions		
General Medicine	Head	Yasuyoshi Ouchi
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	Masatoshi Makuuchi
Stomach and Esophagus Surgery	Head	Michio Kaminishi
Colon and Rectal Surgery	Head	Hirokazu Nagawa
Hepatobiliary Pancreatic Surgery	Head	Masatoshi Makuuchi
Vascular Surgery	Head	Hirokazu Nagawa
Breast and Endocrine Surgery	Head	Michio Kaminishi
Artificial organ and Transplantation Surgery	Head	Masatoshi Makuuchi
Cardiovascular Surgery	Head	Shinichi Takamoto
Thoracic Surgery	Head	Shinichi Takamoto
Neurosurgery		
Anesthesiology and Pain Relief Center Urology and Andrology	Head	Tadaichi Kitamura
Gynecologic Surgery	Head	Osamu Tsutsumi

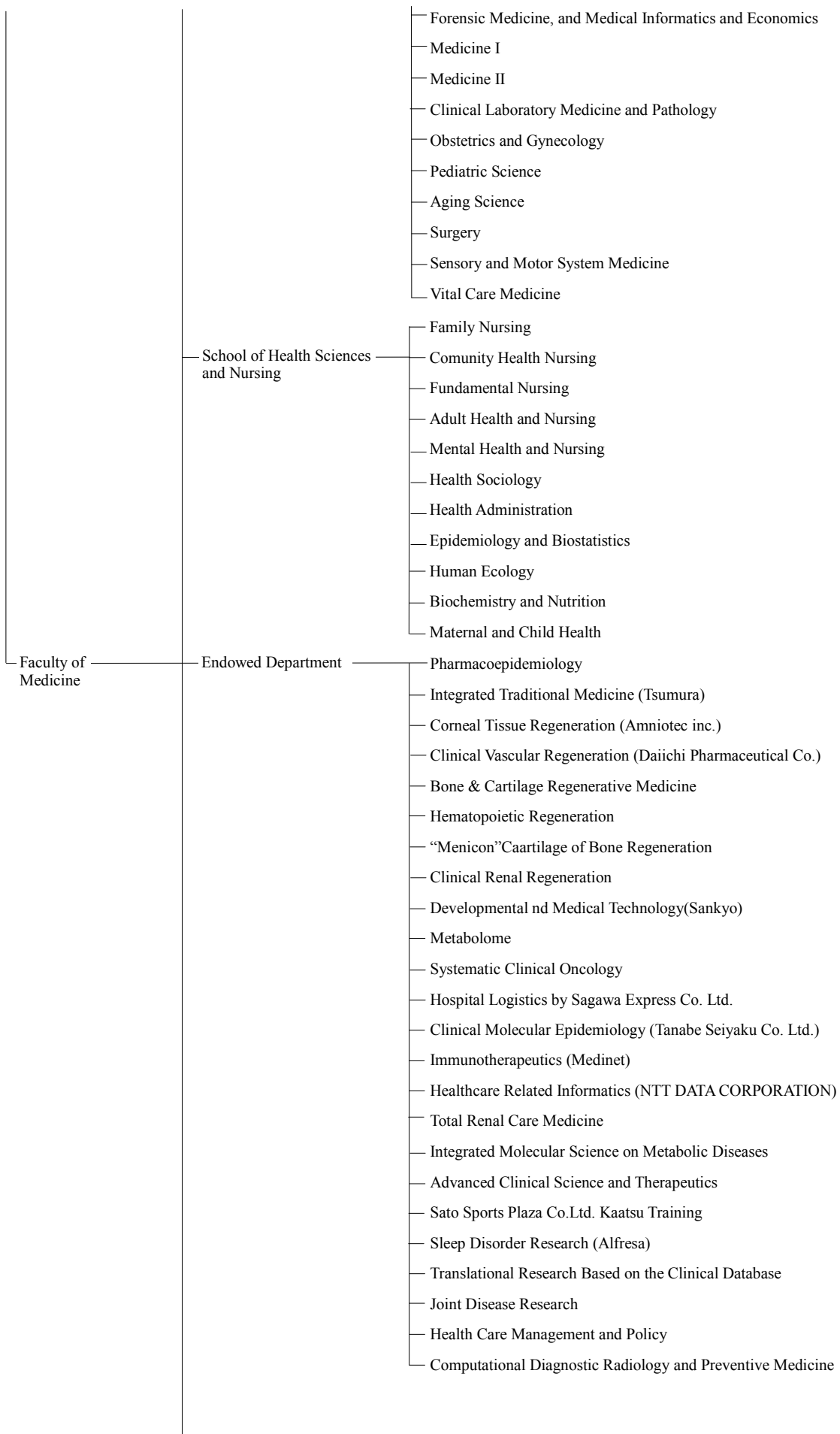
Dermatology and Photolaser Medicine	Head	Kunihiko Tamaki
Ophthalmology and Vision Collection	Head	Makoto Araie
Orthopaedic and Spinal Surgery	Head	Kouzo Nakamura
Otorhinolaryngology and Auditory and Voice Surgery	Head	Kimitaka Kaga
Rehabilitation Medicine		
Plastic, Reconstructive and Aesthetic Surgery	Head	Isao Koshima
Oral-Maxillofacial Surgery, Dentistry and Orthodontics	Head	Tsuyoshi Takato
Pediatrics	Head	Takashi Igarashi
Pediatric Surgery	Head	Kohei Hashizume
Obstetrics and Gynecology	Head	Yuji Taketani
Neuropsychiatry	Head	Nobumasa Kato
Radiology	Head	Kuni Ohtomo
Central Clinical Facilities		
Clinical Laboratory Center	Head	Yutaka Yatomi
Surgical Center		
Radiological Center	Head	Kuni Ohtomo
Emergency Services	Head	Naoki Yahagi
Transfusion Medicine and Immunohematology	Head	Koki Takahashi
Delivery Unit	Head	Yuji Taketani
Rehabilitation Service		
Medical Engineering (tentative name)		
Supply Center (tentative name)		
Intensive Care Unit	Head	Naoki Yahagi
Intensive Pathology	Head	Masashi Fukayama
Corneal Transplantation	Head	Shiro Amano
Infection Control and Prevention	Head	Kazuhiko Koike
Department of Endoscopy and Endoscopic Surgery	Head	Takao Kawabe
Center for Hemodialysis and Apheresis	Head	Toshiro Fujita
University Hospital Medical Information Network Center	Head	Takahiro Kiuchi
Cell Therapy and Transplantation Medicine	Head	Shigeru Chiba
Clinical Research Center(tentative name)	Head	Masao Omata
Department of Medical Social Service and Welfare	Head	Yasuyoshi Ouchi
Department of Planning, Information and Management	Head	Kazuhiko Ohe
Department of Organ Transplantation Service	Head	Masatoshi Makuuchi
Pharmaceutical Department	Head	Hiroshi Suzuki

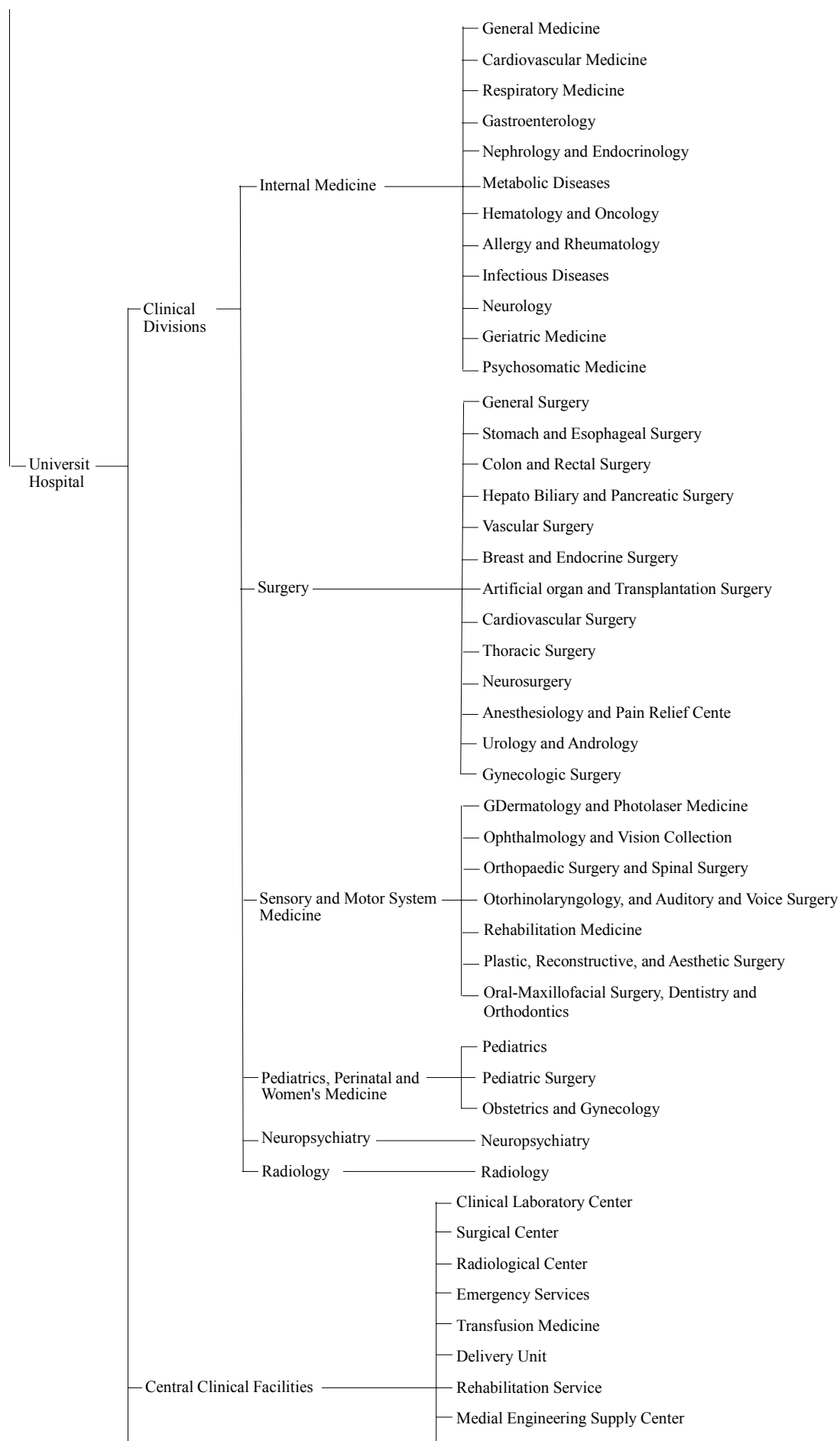
Organization Chart











	Intensive Care Unit
	Pathology
	Sectin of Corneal Transplantation
	Department of Cell and Gene Therapy
	Department of Endoscopy and Endoscopic Surgery
	Department of Hemodialysis and Apheresis
	Hospital Computer Center
	Department of Medical Social Service and Welfare
	Clinical Research Center
	Infection Control and Prevention
	University Hospital Hospital Medical Information Network Center
	Organ Transplantation Service
	Department of Nutrition
	Labor Safety and Health Management Office
	Project Team For Hospital Development
	Department of Clinical and Genetic Informatics
	The Clinical Training Center
	Department of Palliative Medicine
	Public Relations Office
	Department of Clinical Genomics
	Cooperative Unit of Medicine and Engineering Research
Pharmaceutical Department	
Nursing Department	
Administration Office	

History

- 1858 May 82 practitioners trained in Dutch (European) medicine in Edo (Tokyo) laid out money and established at Kanda Mitamagaiké 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 Poniatics 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 Phoniatrics.
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.

**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

Yoshimitsu Kanai, M. D.,
Sen Takeda, M. D.

Takao Nakata, M. D.,

Yosuke Takei, M. D.,

Lecturer

Yasuko Noda, M. D.,

Sumio Terada, M. D.

Associate

Yasushi Okada, M. D.,
Ryo Nitta, M. D.,
Hiroaki Yajima, Ph. D.

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

Masahiko Kawagishi, M. D.,
Harukata Miki, Ph. D.,

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

Teaching activities

Our teaching responsibility is following.

I.

- 1) Lecture on Cell Biology, 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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Molecular Cell Biology

2. Biochemistry and Molecular Biology

Department of Molecular Biology

Professor

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

Associate Professor

Shigeki Jinno, Ph.D.

Associate

Hanako Yamamoto, Ph.D.,

Kenji Ito, Ph.D.

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

Introduction and Organization

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

Professor Muneo Kumagawa, who headed this first Biochemistry or Medical Chemistry Department established in this country, graduated in 1882 The University of Tokyo Faculty of Medicine. In 1884 he went to Department of Pathology, The University of Berlin headed by Rudolf Virchow and under the supervision of Ernst Salkowski. After returning to Japan, he was promoted to Lecture and Professor of this Department. In 1908, He discovered lack of glycogenecity in lipids, which has been firmly established besides some exceptions, and succeeded in purification of vitamin B1, which was discovered by C. Eijkman in 1906. He educated many including Masahiro Sakaguchi, who developed a world-famous colorimetric method for

arginine and Takaoki Sasaki, who first succeeded in generating liver cancer with chemicals.

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

Professors Kodama and Shimazono.

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

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

Professor Tamio Yamakawa graduated The Imperial University of Tokyo Faculty of Medicine and began studies at The Institute for In-

fectious 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. We now have identified the protease as lysosomal cathepsins, released from low cholesterol-content ly-

sosomes upon anchorage deprivation. We further found that the PI3-kinase-mTOR signal was essential for blocking the release of cathepsins from the lysosomes and that anchorage loss disrupted this signaling, thereby inducing cathepsin release and Cdc6 degradation.

2. Transcriptional control of the cdc6 gene

It has been known that the E2F-DP-Rb transcriptional factor complex regulates transcription of the cdc6 gene. We have discovered that a transcriptional activator to be identified is critically involved in activation of this promoter during growth stimulation and that this factor is activated by Cdk4. This finding provides a critical clue to solve the long recognized paradox that functionally similar Cdk4 and Cdk6 are expressed in cells and both can activate E2F-DP-Rb, yet Cdk4 is uniquely required for S phase onset.

3. Mechanism controlling recovery from DNA damage-induced S phase arrest

It has been known that after receiving severe DNA damage, cells are delayed in recovery and resumption of S phase progression long after DNA damage repair is completed. We found that Cdc6 protein plays a critical role in determining the timing of recovery. Enforced expression of Cdc6 drastically accelerates recovery with similarly accelerated reactivation of Cdk2. Thus Cdc6 plays a highly important role in S phase progression even after the assembly of Pre-RC is completed.

Education

To medical students, we give lectures on DNA and related. DNA replication, transcription, nuclear export of mRNA, translation, gene engineering and mobile DNA 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

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

Associate Professor

Takehiko Yokomizo, M.D., Ph.D.

Lecturer

Satoshi Ishii, Ph.D.

Associate

Yoshihiro Kita, Ph.D.,

Hideo Shindou, Ph.D.

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

Introduction and Organization

In addition to the above 5 faculty members, we have 15 graduate students (14 doctor course students including 2 PhD-MD course students and 1 master course student), and 1 undergraduate medical student (Free Quarter). Several clinical scientists and a research fellow from pharmaceutical company are also our members. Ms Toshie Takahashi (Associate) belongs to the Dean of the Faculty and is in charge of maintenance and education of various instruments for common use.

Teaching activities

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 2005 is around 10. For graduate course students, we have three-month lecture series (biochemistry and genetic engineering), and an eight-week laboratory course for clinical scientists.

Research activities

1. Roles and cellular signaling of lipid mediators.
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 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. 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. Metabolomics analyses of lipid mediators.

Lipid mediators are produced through cascade pathways. 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. Research on membrane biogenesis and surfactant production.

Membrane phospholipids and pulmonary surfactants are produced by a family of lysophospholipid acyltransferases. We recently isolated a gene encoding lysophosphatidylcholine acyltransferases, which might be involved in production of pulmonary surfactant.

4. 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.

5. 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 protocols useful for the molecular and cellular biology studies. Drs. Kimura and Kita are responsible for the homepage.

6. 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.

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Department of Physiological Chemistry and Metabolism

Professor

Hiroki Kurihara, M.D.

Associate Professor

Tomoichiro Asano, M.D.

Associate

Yukiko Kurihara, M.D.,

Yasunobu Uchijima, Ph.D.

URL <http://bio.m.u-tokyo.ac.jp/home-j.html>

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 re-named '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, 1 visiting scientist, 10 graduate students (8 doctoral course, 2 master's course). We are also working together with the Endowment Department of Developmental and Medical Technology (Sankyo) in research and education.

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. Development

To clarify the molecular mechanism underlying the morphogenesis and organogenesis in the craniofacial and cardiovascular region, we investigated the phenotype of endothelin-1 (ET-1) knockout mice and identified the ET-1/Dlx5/6 pathway involved in neural crest-driven branchial arch patterning. We are now studying the intracellular signaling pathway involved and the function of downstream molecules including Calpain6. We further identified TAZ as a protein that binds to and coactivates Pax3, a key transcription factor in neural crest development and are analyzing its function in vivo.

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 are getting new findings about the mechanism of maintenance methylation during preimplantation de-

velopment.

In addition, we are investigating the organogenesis and cell differentiation of the vessel, lung and inner ear, aiming at their regeneration. Recently, 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.

2. Metabolism

Regarding the research for metabolism, we identified a novel protein which specifically associates with Akt, a key molecule for insulin-mediated metabolism. This protein enhances the phosphorylation state as well as the kinase activity of Akt, and thus, we termed it as APE (Akt Phosphorylation Enhancer). APE is very likely to be involved in the suppression of apoptosis and regulation of cell cycle, and interestingly, APE overexpression was observed in the approximately half of the cancer cell lines tested.

In addition, we found that resistin like molecule β (RELM β) secreted from gut is increased by high-fat diet or in the obese condition. RELM β activates ERK and JNK, and thereby induces insulin resistance. Indeed, it was demonstrated that RELM β transgenic mice exhibited hyperglycemia, hyperlipidemia and fatty liver. Thus, we speculate that RELM β can be a diagnostic marker for judging insulin resistance, or also be a good candidate as a target molecule for the therapy of insulin resistance. We are currently investigating the effects of RELM β on vascular function and an involvement on atherosclerosis, and also attempting to construct a system for measuring human RELM β .

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Functional Biology

1. Physiology

Department of Integrative Physiology

Professor

Yasushi Miyashita, Ph.D.

Associate Professor

Seiki Konishi, M.D., Ph.D.

Lecturer

Kiyoshi Nakahara, Ph.D.

Associate

Tetsuya Fukushima, M.D., Ph.D., Toshiyuki Hirabayashi, Ph.D.,
Masaki Takeda, Ph.D.

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

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, K. Honma and I. Hasegawa) 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 organiza-

tions of living systems. The curriculum is updated every year. For example, a new electrocardiogram experiment in humans was introduced to the laboratory course, which gained popularity and interest among students. We accept *Free-Quarter* students every year. Usually these students' activities are not limited to one *Quarter*, and 3 students (M0, M2 and M3) continued to enjoy their research from 2004 through 2005. Some of these students completed their own projects, and gave oral presentations in international meetings and published original papers in top-rank international journals.

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. Recently many functional subfields have been identified in the occipito-temporal 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. In particular, fMRI with the echo-planar magnetic resonance sequence provides a powerful noninvasive method that is superior to conventional PET imaging in both spatial and temporal resolution. FMRI is completely noninvasive and appro-

priate for use with normal volunteers. We developed 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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Department of Cellular and Molecular Physiology

Professor

Kensaku Mori, Ph.D.

Lecturer

Masahiro Yamaguchi, M.D., Ph.D.

Associate

Hiroshi Nagao, Ph.D.,

Hideki Kashiwadani, Ph.D.

Homepage [http:// morilab.m.u-tokyo.ac.jp/](http://morilab.m.u-tokyo.ac.jp/)

Education

The department provides lectures and practice in physiology for undergraduate 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.

We have been investigating also the functions of cell adhesion molecules in the development of synapses and neuronal circuits as well as in the contact-mediated interactions between neurons and immune cells.

Currently we are focusing on the following four

topics.

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

We are studying the ‘odor maps’ in the olfactory bulb and olfactory cortex to understand the logic employed by the olfactory system for discrimination among numerous odor molecules and perception of the olfactory image of objects. Recently we demonstrated a powerful state-dependent gating of odor information flow within olfactory cortex that works in synchrony with the gating of other sensory systems. Our findings suggest a state-dependent switchover of signal processing modes in olfactory cortex, and open the way to analyzing the gating in olfactory system.

- (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 found that damage on hippocampal CA1 area caused by local injection of kainic acid increased density and area of contacts between activated microglia and the dendrites of CA1 pyramidal neurons. We are further investigating the telen-

cephalin-mediated signals between neurons and immune cells during recovery from the neuronal damage.

(3) Neurogenesis and neuron-elimination in the adult brain.

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. We are also focusing on the heterogeneity of local interneurons in the olfactory bulb. We are trying to reveal the functional differentiation of subtypes of interneurons in odor information processing, and address the question how they are recruited into the adult neuronal circuit and contribute to the plasticity of adult olfactory system.

(4) Molecular and cellular mechanisms for the formation and plasticity of specific neuronal connections.

Olfactory system has precise projection of olfactory axons onto specific glomeruli and distinct neuronal circuit with laminar specific synaptic connections. We found that a leucine rich repeat membrane protein, 5T4, was expressed by a specific subset of granule cells, whose dendrites project selectively to the superficial sublamina of the external plexiform layer. The results suggest that 5T4-positive granule cells preferentially interact with tufted cells. We will expand the investigation to the other candidate molecules already found by the proteomics approach.

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Department of Neurophysiology

Professor

Tomoyuki Takahashi, M.D., Ph.D.

Lecturer

Tetsuhiro Tsujimoto, M.D., Ph.D.

Naoto Saitoh, Ph.D.

Associate

Tetsuya Hori, Ph.D.

Home page <http://square.umin.ac.jp/nphystky>

Introduction and organization

Our 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 is aimed at elucidating cellular and molecular mechanisms underlying synaptic transmission.

Teaching activities

We teach medical undergraduates in lectures and a practical course. Lectures are designed for students to learn basic mechanisms underlying electrical signals, how they are generated and propagated through nerve fibers and across synapses. Students also learn dynamic aspects of synaptic efficacy underlying diverse brain functions such as memory and consciousness. A couple of months before lectures students in 20 groups are given key words with references to prepare a summary sheet, upon which each group presents a short talk in a class. Their talks are followed by discussions and supplementary lectures by a professor. During the procedure of preparing summary sheets, students make discussions with a professor. In practical course, students are encouraged to make patch-clamp recordings from neurons visually identified in brain

slices. In this course, students learn how electrical signals are made of ion channel currents. In separate set-ups, students record field synaptic potentials from hippocampal slices and learn how to induce short-term and long-term Ph.D. synaptic plasticities. Trainings for the Master and Ph.D. course students are made regularly on Monday in the forms of progress reports and journal clubs, where students and staffs summarize topics and also classics in physiology and neuroscience.

Research Activities

In mammalian CNS, after synaptic contacts are formed in fetal period, synapses undergo morphological, functional and molecular changes during postnatal development, toward establishment of mature synapses differentiated into various neuronal functions. Our research aim is to clarify causal molecular-functional relationship, for elucidating molecular mechanisms underlying synaptic transmission and modulation. In brainstem slices of rodents, a giant nerve terminal, called the calyx of Held, can be visually identified. We make simultaneous presynaptic and postsynaptic whole-cell recordings from the calyces and target cells in developing rodents, and make analyses on synaptic transmission. With these recordings we combine (i) presynaptic capacitance measurements for assessing synaptic vesicle exo/endocytosis, (ii)

infusion of drugs or inhibitor proteins into the terminal, (iii) Ca measurements. In addition we make (iv) immunocytochemical examinations for protein expressions in the calyceal terminals, (v) use knockout mice to establish causal molecular-function relationships, and (vi) make bilateral cochlear ablations to investigate whether newly found developmental change depends upon hearing input activity. Our present subjects of research are clarifications of mechanisms underlying (1) vesicle recycling and re-use, (2) transmitter release probability, (3) facilitation of transmitter release, (3) high-fidelity synaptic transmission.

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Functional Biology

2. Pharmacology

Department of Cellular and Molecular Pharmacology

Professor

Masamitsu Iino, M.D., Ph.D.

Associate Professor

Kenzo Hirose, M.D., Ph.D.

Associate

Toshiko Yamazawa, Ph. D.,

Sho Kakizawa, Ph. D.

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

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

Research activities

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 central neurons.

Ca^{2+} signals show very dynamic, temporal and spatial changes. This property allows the calcium 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. 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.

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. Recently, 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.

The RNA interference technique is an extremely useful method to knock down target mRNA to study the function of the protein in question. We generated a new method for enzymatic production of libraries of small interfering RNA. In addition, in collaboration with outside research groups, we looked into the molecular mechanism of circadian rhythm.

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Department of Molecular Neurobiology

Professor

Masayoshi Mishina, Ph.D.

Associate

Tomonori Takeuchi, Ph.D.,

Takashi Uemura, Ph.D.,

Tomoyuki Yoshida, Ph.D.,

Kazuto Nakao, Ph.D.

Homepage <http://www.pharmacol2.m.u-tokyo.ac.jp/>

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 basis of learning and memory. As an initial step, we have elucidated the molecular diversity of the NMDA-type glutamate receptor (GluR) channel that plays a key role in synaptic plasticity as a molecular coincidence detector. Combination of the GluR ϵ and GluR ζ subunit families is essential for the formation NMDA-type GluR channels. The four glutamate-binding GluR ϵ subunits are distinct in distribution,

functional properties and regulation. Thus, multiple GluR ϵ subunits are major determinants of the NMDA receptor channel diversity, and the molecular compositions and functional properties of NMDA receptor channels are different depending on the brain regions and developmental stages. We generated mutant mice defective in respective GluR ϵ subunits by gene targeting. We have shown that disruption of the GluR ϵ 1 subunit results in the increase of thresholds for both hippocampal LTP and contextual learning. The GluR ϵ 2 subunit mutant mice showed the impairment of the formation of the whisker-related neuronal barrelette structure in the brainstem trigeminal nucleus. We found the GluR δ subunit family, a novel member of the GluR channel family, by cloning. The GluR δ 2 subunit is selectively localized in cerebellar Purkinje cells. Analyses of the GluR δ 2 mutant mice reveal that the δ 2 subunit plays important roles in the motor coordination, the formation of parallel fiber-Purkinje cell synapses and climbing fiber-Purkinje cell synapses, and the long-term depression of parallel fiber-Purkinje cell synaptic transmission. These findings have led our current hypothesis that the activity-dependent synapse refinement during neural development and the learning and memory in adult brain share the common molecular mechanism.

To verify this proposal, we are employing two approaches. One is the forward genetic approach in zebrafish to systematically screen the key molecules of

the formation and dynamic changes of synapses. We developed a highly efficient deletion mutagenesis in zebrafish and isolated mutant zebrafish with defects in neural development. Current efforts are on the efficient cloning of the mutant genes. The other approach is the reverse genetics with mice. To examine the functional roles of developmentally important molecules in higher brain functions and to seek for engram, we are developing the stage- and brain region-specific conditional targeting. The wealth of knowledge on the neural circuits makes the cerebellum an ideal system to study the molecular mechanism of brain function. To develop a cell type-specific and temporal regulation system of gene targeting in the cerebellum, we employed the NMDA-type glutamate receptor GluR ϵ 3 subunit gene and Cre recombinase-progesterone receptor fusion (CrePR) gene in combination. Injection of the CrePR fusion gene placed under the control of the 10 kb 5' region of the GluR ϵ 3 gene into C57BL/6 eggs yielded the ECP25 line that strongly expressed the CrePR mRNA selectively in the granule cells of the cerebellum. Using a transgenic mouse carrying a reporter gene for Cre-mediated recombination, we showed that antiprogesterins could induce the recombinase activity of CrePR fusion protein in the cerebellar granule cells of the ECP25 line. Thus, the established mouse line will provide a valuable tool to investigate the mechanism of cerebellar function by manipulating molecules in the temporally regulated and granule cell-specific manner

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Pathology, Immunology and Microbiology

1. Pathology

Department of Human Pathology and Diagnostic Pathology

Professor

Masashi Fukayama, M.D., Ph.D.

Associate Professor

Toshiro Niki, M.D., Ph.D. (Professor, Jichi Medical School),

Ken-ichi Ohashi, M.D., Ph.D. (Toranomon Hospital)

Lecturer

Noriyoshi Fukushima, M.D., Ph.D., Hiroshi Uozaki, M.D., Ph.D.

Ja-Mun Chong, M.D., Ph.D. (visiting researcher, USA),

Hisako Endo, M.D., Ph.D. (Division of Diagnostic Pathology)

Lecturer (Hospital)

Kenji Kashima, M.D., Ph.D.,

Yutaka Takazawa, M.D., Ph.D.

Toru Motoi, M.D., Ph.D. (visiting researcher, USA)

Associate

Satoshi Ota, M.D., Ph.D.,

Tateru Ishida, M.D., Ph.D.

Akiteru Goto, M.D., Ph.D.,

Junji Shibahara, M.D., Ph.D.,

Tetsuo Ushiku, M.D., Ph.D.

Yasunori Ota, M.D., Ph.D. (Toranomon Hospital)

Technical Support Specialist

Takamichi Natsuzaka,

Yasuyuki Morishita, M.T.,

Shinichi Harada

Homepage <http://pathol.umin.ac.jp/>

Introduction and Organization

The Department of Human Pathology united the Department of Diagnostic Pathology, and has started as a new department, the Department of Human Pathology and Diagnostic Pathology in 2003. It is responsible for the practice of diagnostic pathology, education, and research in conjunction with Division of Diagnostic Pathology of the University Hospital. The unification is also expected to facilitate the next-generation pathology.

We celebrated the 30th memorial year of the Division of Diagnostic Pathology, and published commemorative issues in 2005. We also hosted the 51st autumn scientific meeting of Japanese Academy of Pathology at Yasuda Memorial Hall.

The staffs in 2004 consisted of a professor, (MF), two associate professors (TN, KO), four associates (KK, AG, JS, TU) and three technical support specialists (TN, YM, SH). The staffs of Division of Diagnostic Pathology (DDP) were one lecturer (HE), and four associates (TM, HU,

YT, YO). In 2005, the associate professor, Dr. T Niki was invited as the professor by Jichi Medical School. Dr. K Ohashi moved to Toranomon Hospital as the Director of Department of Pathology, and Dr. Y Ota also moved to the Toranomon Hospital. Lecturer Dr. N Fukushima came from Tokyo Medical School, and Dr. H Uozaki was promoted to a Lecturer. Dr. S Ota came from Division of Pathology, Hokkaido University Hospital, and Dr. T Ishida from Department of Hematology, Juntendo University. Dr. H Endo will complete her term of office at the end of this fiscal year.

Two graduates received PhD in 2004 and six in 2005. Twelve postgraduate students (one from other university and three from abroad) are now studying in the department.

We are responsible for the surgical pathology and autopsy in the University Hospital. The research is based on morphology, targeting human diseases. On the other hand, we take charge of Systemic Pathology course, Clinical Clerkship, and Bedside-learning for 2nd–4th grade students. We also take part in the General Pathology course in conjunction with Department of Molecular Pathology.

Clinical activities

The surgical pathology practice and autopsy services are our duties. We are now engaged in the technical and systemic development of rapid diagnosis, utilizing the rapid tissue processing system.

Autopsy conference on two cases each is regularly held every month. CPC is also held periodically for surgical pathology including tumors of thoracic organs and upper gastrointestinal tract, brain, liver, pancreatobiliary tract, urology, gynecology, bone- and soft tissue, and biopsy of various disease of liver, kidney, & dermatology.

Teaching activities

We take part in the General Pathology course, especially in its morphological aspects for the

1st grade of undergraduate students. The course program and lecture notes are available in UT Open Course Ware (<http://ocw.u-tokyo.ac.jp/>) .

Classes of Systemic Pathology course and exercises are now held every week in parallel with those of Systemic Medical course. Such an integrated classes are expected to promote the students' understanding. We have prepared the pathology lectures for ophthalmology, oral surgery, and otolaryngology. Pathology exercises for brain tumors, dermatology, and infectious diseases are also included. We have adopted the slide-projected examination since 2003, and the questions and answers are available on our website.

In BSL course, a pair of students is required to inspect and analyze the one teaching case of autopsy. Students are also required to examine surgical materials of popular Carcinomas. One-month course of Clinical Clerkship has been introduced since 2003. Seven students took the course from January to March in 2004, and the same in 2005.

The past graduate examinations of Diagnostic Pathology are also referred on the web. We owe the development and maintenance of our web-site to Dr. Uozaki.

Research activities

Armed with the morphology, we are engaged in the investigation of the relationship between chronic inflammation and neoplasm:

1. Epstein-Barr virus associated neoplasms, such as gastric carcinoma and lymphomas. .
2. Lung carcinomas and scar formation.

We are also searching the candidates for the antibody drug by global analysis of expression profiles of various cancers in collaboration with Research Center for Advanced Science and Technology, the University of Tokyo.

Our research lab has moved to the new building in December, 2005. Although the research style of human pathology is a ranch-type, rather than a factory-type, the standard research facilities of molecular biology and molecular pathology are indispensable. Dr. Ka-

shima devoted himself to set up our laboratory.

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- 2005
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Department of Molecular Pathology

Professor

Kohei Miyazono, M.D., D.M.S.

Associate Professor

Keiji Miyazawa, Ph.D.

Associate

Masao Saitoh, D.D.S.

Tetsuro Watabe, Ph.D.

Homepage <http://beta-lab.umin.ac.jp/>

Introduction and Organization

Our department has a more than 100-year history from its establishment as the Department of Pathology. Prof. Miyazono started to work as the professor of the Department of Molecular Pathology in August 2000. Now, the Department consists of a professor, an associate professor, two associates, 4 technicians, and several research fellows, including 6 graduate students, 5 master course students, 2 post-doctoral fellows, and a research fellow from France.

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 spend some time for lectures on a series of basic tumor biology in our lectures. 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, “Journal Club” every Friday, and “Monday Seminar” once a month in collaboration with the Department of Biochemistry at the Cancer Institute of the Japanese Foundation for Cancer Research.

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.

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)- β superfamily 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.

Since TGF- β is a potent inhibitor of various cells, perturbations of TGF- β signaling result in progression of cancer. On the other hand, TGF- β accelerates growth and metastasis of certain cancers in advanced stages. Thus, studies on the mechanisms of TGF- β signaling is important to understand the roles of TGF- β in various cancers. We are currently interested in mechanisms of the action of inhibitory Smad (Smad7) and transcriptional co-repressor c-Ski in TGF- β signaling. We have found that the activity of Smad7 is positively regulated by ubiquitin ligases Smurf1/2 and WWP1, whereas another ubiquitin ligase Arkadia negatively regulates the action of Smad7. We have also shown that transfer of the Smad7 gene results in prevention of metastasis of murine breast cancer. BMPs are members of the TGF- β superfamily. We have reported that BMP-4 induces apoptosis of myeloma and B-cell hybridoma cells by dysfunction of the endoplasmic reticulum.

While lymphatic systems play important roles in physiological conditions and pathological processes such as cancer metastasis, molecular mechanisms that govern lymphangiogenesis remain largely unknown. We have found that homeobox transcription factor Prox1 induces expression of VEGF receptor-2, PDGF receptor- β , and Angiopoietin-2 in endothelial cells, resulting in enhancement of motility and migration of endothelial cells. Prox1 thus acts as a master regulator of lymphangiogenesis, and confers the characteristics of lymphatic endothelial cells to vascular endothelial cells by modulating multiple signaling cascades.

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Pathology, Immunology and Microbiology

2. Microbiology

Department of Microbiology

Professor

Akio Nomoto, Ph.D.

Associate Professor

Tetsuro Matano, M.D., Ph.D.

Associate

Takeshi Yamada, Ph.D.,

Tsubasa Munakata, Ph.D.,

Seii Ohka, Ph.D.

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

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.

Teaching Activities

Undergraduate Course, Faculty of Medicine

In a series of lectures (totally 60 hr) and laboratory courses (30 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 Institutes of Infectious Diseases (Dr. Shimada), Dokkyo Medical University (Dr. Masuda), Teikyo University (Dr. Kawana), Faculty of Agriculture (Dr. Onodera), and Institute of Medical Science (Dr. Sasakawa, Dr. Kawaoka, Dr. Iwamoto, and Dr. Saito) contribute to the teaching activities.

Research Activities

1. **IRES (internal ribosome entry site)-dependent virus tropism**
Ohka, S., Azuma, A., Murakami, K., Fujimaki, T., Munakata, T., Honaga, T., Yanagiya, A., and Nomoto, A.
2. **Poliovirus entry via PVR (poliovirus receptor)**
Ohka, S., Matsuda, N., and Nomoto, A.
3. **Effect of viral infection on cell metabolism**
Matsuda, N., Yanagiya, A., Ohka, S., and Nomoto, A.
4. **Blood brain barrier permeation of poliovirus**
Sakai, M., Ohka, S., and Nomoto, A.
5. **HCV (hepatitis C virus) genome as an RNA replicon**

- Yamada, T., Shigenobu, F., and Nomoto, A.
6. **Molecular basis for HCV pathogenesis**
Yamada, T., Murayama, A., and Nomoto, A.
 7. **Molecular basis for retroviral pathogenesis**
Kawada, M., Kusuki, K., Shoto, S., Sasaki, Y., Seki, S., Takeda, A., Igarashi, H., and Matano, T.
 8. **Virus-specific immune responses**
Tsukamoto, T., Kawada, M., Kobayashi, M., Takeda, A., Igarashi, H., and Matano, T.
 9. **Development of AIDS vaccine**
Yamamoto, H., Moriya, C., Kato, M., Takeda, A., Igarashi, H., and Matano, T.

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- Matano T. Reversion in vivo after inoculation of a molecular proviral DNA clone of simian immunodeficiency virus with a cytotoxic-T-lymphocyte escape mutation. *J Virol.* 2005;79:11529-32.
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Department of Infection Control and Prevention

Professor

Kazuhiko Koike, M.D., Ph.D.

Lecturer

Kyoji Moriya, M.D., Ph.D.

Hiroshi Yotsuyanagi, M.D., Ph.D.

Associate

Yoshizumi Shintani, M.D.,

Shu Okugawa, M.D., Ph.D.

Homepage <http://www.cc.h.u-tokyo.ac.jp/mulins/kansen/index.html> (inside the hospital only)

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 associates, one research student, 12 laboratory technicians, and two office assistants. For isolation and identification of microorganisms from clinical specimens, we amalgamated the microbiology unit from the Department of Clinical Laboratory in 2001.

Clinical activities

Our daily activities are as follows:

- 1) Surveillance and control of hospital-acquired infection, such as infection or colonization of methicillin-resistant *Staphylococcus aureus* and other drug-resistant microbes.
- 2) Investigation of trends in weekly bases and monthly reports to all departments; Screening of

colonization; monitoring of appropriate use of antibiotics 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

Department of Immunology

Professor

Tadatsugu Taniguchi, Ph.D.

Lecturer

Akinori Takaoka, M.D., Ph.D.

Associate

Kenya Honda, M.D., Ph.D.,

Hideyuki Yanai, Ph.D.

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

Introduction and Organization

The Department of Immunology was formerly called the Department of Serology, which has a history going back to 1918. The department was changed to its present name, when Dr. Tomio Tada, now Professor Emeritus of The University of Tokyo, took his position in 1977 as the professor and chair of the department. Dr. Tada has made great contributions that made this department world-renowned, through his innovative research as well as his great contributions to the international community of immunologists. After his retirement in 1994, we basically followed the tradition of the department established by Dr. Tada and tried to improve it further, in terms of providing high-standard education to students and cutting-edge research in immunology worldwide. Research projects currently being conducted began with the original identification of two cytokine genes and their characterization between the late 1970s and the early 1980s, namely, the genes encoding human fibroblast interferon (now known as IFN- γ) and interleukin-2 (IL-2). These initial studies have led us to further characterization of these cytokine systems in the context of the regulation of immunity and oncogenesis. One of our major contributions is

the discovery and characterization of a new family of transcription factors, termed interferon regulatory factors (IRFs). Our current research interests are aimed at clarifying the function and regulation of the IRF family of transcription factors in oncogenesis and immunity. As a part of our scientific and educational activities, we organize many seminars by inviting distinguished scientists from all over the world..

Teaching activities

Our teaching responsibility is to provide lectures on immunobiology, immunochemistry and molecular immunology to the undergraduate students of the faculty. It is also our responsibility to provide laboratory courses on basic immunology to students. In addition to lectures and laboratory courses provided by our own staff members, special lectures are also given by guest experts. We also offer a special training course (called 'free quarter') of basic and advanced biological and immunological techniques to medical students. The education of graduate students is based on weekly conferences during which the students present the progress of their own research projects and discuss on their future directions. Lectures on

leading research activities are given by active researchers from overseas whenever they visit our department. The students may gain a profound interest in the field through these lectures.

Research activities

Our research field includes cellular and molecular immunology in general. Once an immune response is initiated by an antigenic stimulus, the magnitude of the response is controlled by the complex mechanisms. We have been extensively analyzing mechanisms that function in the regulation of gene expression and signal transduction in host defense systems. In particular, we focus on the molecular mechanisms underlying host defense against viral and bacterial infections. Among these mechanisms, the interferon (IFN) system is the most powerful and important for the control of such infections. During the course of the study, we have identified the interferon regulatory factor (IRF) family, which play critical roles in immunity. Most notably, studies of IRFs have revealed their remarkable functional diversity in regulating the immune systems, in particular, as the key regulators of the TLR-induced immune response. We showed that the transcription factor IRF-7 is essential for both the virus-activated MyD88-independent pathway as well as the TLR-activated MyD88-dependent pathway of IFN- α/β gene induction. Furthermore, we found that the MyD88-dependent IFN induction pathway activated in plasmacytoid dendritic cells (pDCs) by the TLR9 family is entirely IRF-7-dependent and this MyD88-IRF-7 pathway is critical to the induction of CD8⁺ T cell response in vivo. The high IFN- α/β production in plasmacytoid dendritic cells (pDCs) induced by the stimulation of the TLR9 subfamily is dependent on the MyD88-IRF-7 signalling pathway; however, it remained unknown until recently how and why pDCs, but not other cell types such as conventional DCs (cDCs), achieve the activation of this pathway. We found that the endosomal persistence of

MyD88-IRF-7 signalling critically determines the unique ability of pDCs to produce large amounts of IFN- α/β . This ingenious spatial regulation of signalling in pDCs represents a distinct response to pathogen-associated nucleic acids that could be exploited for the manipulation of immune responses.

We also found that IRF-5 is essential for the MyD88-dependent gene induction program, which is commonly activated by TLRs. IRF-5 interacts with and is activated by MyD88 and TRAF6, and that TLR activation results in the nuclear translocation of IRF-5 to activate cytokine gene transcription. Thus, our study identified IRF-5 as a new, principal downstream regulator of the TLR-MyD88 signalling pathway and a potential target of therapeutic intervention to control harmful immune responses. More recently, we found that IRF-4 functions as a negative regulator of IRF-5 by competing with IRF-5 for MyD88 interaction. Work is in progress to elucidate further the mechanism of activation of IRF-5, as well as its role in anti-tumor immune responses.

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Radiology and Biomedical Engineering

1. Radiology

Department of Radiology

Professor

Kuni Ohtomo, M.D.,Ph.D.

Associate Professor

Toshimitsu Momose, M.D.,Ph.D.,
Keiichi Nakagawa, M.D.,Ph.D.

Shigeki Aoki, M.D.,Ph.D.,

Lecturer

Osamu Abe, M.D.,Ph.D.,
Masaaki Akahane, M.D.,

Masao Tago, M.D.,Ph.D.
Yoshitaka Masutani, Ph.D.

Associate

Hisao Koga, M.D.,
Hiroshi Igaki, M.D.,Ph.D.,
Nobuyuki Kato, M.D.,

Haruyasu Yamada, M.D.,Ph.D.,
Harushi Mori, M.D.,
Naoki Nakamura, M.D.

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

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 associate) 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, gastro-

enterologists and cardiologists mainly perform interventional procedures.

In the section of Nuclear Medicine, there are two SPECT rooms and two 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 radionuclide (RN) therapy in the same floor. In addition, four beds are allotted to terminal care ward located in the 14th floor.

Teaching activities

Lectures are given to the fourth-, fifth- and sixth-year students to provide fundamental knowledge of diagnostic radiology, radiation oncology and nuclear medicine. Professor, associate professors and lecturers as well as specialists assigned as part time lecturers take part in the education. A series of lectures about fundamentals of radiology and related sciences are given to the fourth-year students. As bedside-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 softwares to abstract clinically useful information from the 3D imaging data more sophisticatedly. In the field of magnetic reso-

nance (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

2. Biomedical Engineering

Department of System Physiology

Professor

Joji Ando, M.D., Ph.D.

Lecturer

Masahiro Shibata, Ph.D.,

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

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

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 two lecturers.

Teaching activities

We provide lectures of “Early Exposure to Medicine” for second year students, “Basic Principles of Biomedical Engineering” for second and third year students, “Introduction to Biomedical Engineering” for postgraduate 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
4. Oxygen dynamics and microvascular energetics

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).

2. Shear stress-mediated gene regulation

We have demonstrated that shear stress regulates endothelial gene expression transcriptionally and/or post-transcriptionally. Shear stress downregulates VCAM-1 gene transcription via the double AP-1 binding element (TGACTCA) in the promoter which functions as a shear stress-responsive element (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).

3. Shear stress signal transduction

We first showed that Ca²⁺ signalling 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 Ca²⁺ response, and at several hundred nanomolar of ATP, intracellular Ca²⁺ concentrations increase in a shear stress-dependent manner (BBRC 1991, 1993). Generally, flow-induced Ca²⁺ responses are initiated at a locus at the cell edge and propagate throughout the entire cell in the form of a Ca²⁺ wave. The initiation locus corresponded precisely to caveolae rich cell edges (Proc Natl 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 Ca²⁺ response (Circ Res 2000). Endogenously released ATP by shear stress is involved in the P2X4-mediated Ca²⁺ responses (Am J

Physiol 2003). Recently, 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).

4. Oxygen dynamics and microvascular energetics

For nearly 100 years, the capillary is believed to be the sole source of oxygen supply to surrounding tissue. By using an originally developed laser microscopic system (Med Biol Eng Comput 1999), we found a significant downstream drop in the arteriolar oxygen level (J Appl Physiol 2001), and clarified that this drop in oxygen was caused by oxygen supply to tissue from arterioles (Eur J Appl Physiol 2005). Furthermore, we have examined the effect of vessel wall oxygen consumption on the oxygen drop in arterioles. We found that the vascular wall oxygen consumption in functional arterioles was more than 100 times greater than the values reported in *in vitro* experiments, and the oxygen consumption depends on the total amount of workload of vascular smooth muscle (Am J Physiol 2005a). We have also studied the relationship between the endothelium derived nitric oxide and oxygen transport to tissue, and clarified the physiological role of nitric oxide as a modulator of tissue oxygenation by reducing oxygen consumption by vessel walls (Am J Physiol 2005b).

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Department of Bioimaging and Biomagnetics

Professor

Shoogo Ueno, Ph.D.

Associate

Masaki Sekino, Ph.D.

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

Introduction and Organization

Since its establishment in 1974, the Department of Bioimaging and Biomagnetics has been engaged in research on engineering science in medicine and biology. We promote interaction with the international biomedical research community by hosting and collaborating with distinguished scientists and by participating in domestic and international conferences.

Teaching activities

The faculty and staff of the Department strive to provide the highest quality of education and research opportunities for our students. We are responsible for a lecture on the fundamental engineering principles for medical students, as well as for a lecture on biological engineering for engineering students at the graduate level. In addition to our weekly lectures, the Department has several special lectureships on biomagnetism.

Research activities

Our laboratory specializes in biomagnetic research, which includes the measurement of biomagnetic fields, magnetic stimulation of the brain, and the effects of magnetic fields on biological systems. We develop, integrate, and apply new ideas through innovative interdisciplinary research approaches. Our research topics cover wide areas in medical and biological engineering,

including technology for measurement, information processing, and modeling in the following fields.

1. Magnetic stimulation of biological systems:

- Noninvasive focal and vectorial transcranial magnetic stimulation of the human brain and nervous system.
- Functional mapping of the human cortex by transcranial magnetic stimulation (TMS).
- Calculation and imaging of induced electric fields and currents in the head.
- Modulation of gene expression, such as down-or-up regulation of messenger RNA from repetitive magnetic stimulation.
- Application of repetitive transcranial magnetic stimulation (rTMS) for the treatment of central nervous system diseases and mental illnesses.

2. Measurement of biomagnetic fields:

- Utilization of superconducting quantum interference device (SQUID) to measure the very weak magnetic fields of the brain.
- Source estimation from magnetoencephalographic (MEG) data.
- Studies of higher brain functions, such as memory, cognition, emotion and learning, using MEG, EEG and functional magnetic resonance imaging (fMRI).
- Source modeling of MEG and EEG activities.

3. Effects of magnetic and electromagnetic fields on biological systems and materials:

- Effects of intense magnetic fields on biological materials such as diamagnetic water, fibrin, colla-

gen and paramagnetic oxygen.

- Effects of magnetic and extremely low frequency (ELF) electromagnetic fields on living systems such as developing embryos, genetic systems and intracellular signal transduction.
- Effects of pulsed and electromagnetic fields on living systems such as blood brain barrier, neuronal information processes and carcinogenesis.
- Effects of magnetic fields on biochemical and chemical reactions.
- Applications in tissue engineering.

4. Imaging of Electrical Information Based on Magnetic Resonance Imaging (MRI):

- Impedance MRI
- Direct Neuronal Current MRI

In the past 2 years, our research focused on the development of functional brain dynamics imaging with high time resolution and high spatial resolution. The main techniques employed were TMS (transcranial magnetic stimulation), MEG (magnetoencephalogram), EEG (electroencephalogram), electric current imaging by MRI, and impedance imaging by MRI. These techniques are noninvasive and very useful for studying higher brain functions of humans such as memory and cognition.

- Conventional MRI does not reveal information about the electrical properties of the body. We developed new methods to visualize neuronal current distribution and electrical-impedance distribution. The basic principle is to erase the effects of BOLD (blood oxygenation level dependent) by subtracting MRI signals with different polarities of gradient magnetic fields. Measurements were made with an echo planar imaging (EPI) sequence at 1.5 T. MRI mapping of the neuronal currents in the brain during middle finger and thumb tapping was clearly observed. The basic idea of impedance imaging is to use the shielding effects of induced eddy currents on spin precession.
- We compared current density distributions in electroconvulsive therapy (ECT) and TMS using the finite element method. In the ECT model, electric currents were applied through electrodes with a voltage of 100 V. In the TMS model, an alternating current was applied to a figure-eight coil so that the peak magnetic flux density at the coil center was 0.6 T. The maximum current densities inside the

brain in ECT and TMS were 234 A/m^2 and 322 A/m^2 , respectively. While the skull significantly affected current distributions in ECT, TMS efficiently induced eddy currents in the brain. Our results will support clinical investigations to determine the electrode and coil positions that maximize efficacy.

- We developed an EEG measurement system that combined TMS. We were able to non-invasively evaluate the cortical reactivity and functional connections between different brain areas. We used TMS to investigate memory encoding and retrieval, particularly the role of the dorsolateral prefrontal cortex in associative memory for visual patterns. TMS disrupts associative learning for abstract patterns over the right frontal area, and suggest that the participating cortical networks may be lateralized in accordance with classic concepts of hemispheric specialization.
- To investigate the safety aspects of TMS on the brain, functional and anatomical changes in the brain were investigated. Our initial experimental results revealed that TMS does not affect the fEPSP (field excitatory post synaptic potential) of the rat hippocampus.

We also investigated the effects of strong magnetic fields (8T, 14T) on the structure, organization, and function of biological systems and materials, and the possible medical and therapeutic applications of magnetic fields.

- Animal experimental results. (1) We investigated the cleavage patterns of *Xenopus laevis* eggs in the early stages of development. We observed a declined third cleavage line after exposure to a horizontal strong magnetic field of 14 T. (2) The body temperature of rat decreased by 1 K during magnetic field exposure at 8 T. (3) Near infrared light absorption measurements of a rat brain under strong magnetic fields indicated an increased population of oxygenated hemoglobin. (4) In frog sciatic nerve experiments, nerve conduction velocity was decelerated by magnetic fields of up to 8 T.
- The effects of 14 T strong static magnetic fields on the functional properties of biological materials, such as proteins, oxygen molecules and water, were also investigated. (1) A spectrum profile of hemoglobin inside red blood cells indicated conforma-

tional changes depending on the magnetic flux density. (2) Magnetic field exposure initiated platelet aggregation with the aid of collagen and accelerated the aggregation of platelets and fibrin. (3) Leukemia cell proliferation was decreased by an 8 T magnetic field, as a result of behavioural changes of dissolved oxygen during exposure. (4) Magnetic fields inhibited bioluminescence of luciferin and luciferase in both in vitro and in vivo experiments. Possible applications of magnetic fields for the control of biochemical reactions were suggested.

- We explored the possible medical applications of magnetically oriented collagen. Magnetically oriented collagen fibers were used to control the specific orientation of smooth muscle cells (A7r5), bone cells (MC3T3) and nerve cells (PC12). Further experiments, however, demonstrated the magnetic orientation of adherent cells without collagen guidance after long-term exposure to static magnetic fields. Further studies must be carried out to clarify the detailed mechanisms which include the diamagnetic properties of the cells. Our findings may lead to a clinically viable treatment of bone fractures and bone defects.

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Department of Biosystem Construction & Control

Associate Professor

Yusuke Abe, M.D., Ph.D.

Lecturer

Takashi Isoyama, Ph.D.

Associate

Shuichi Mochizuki, M.D, Ph.D.

Homepage <http://www.bme.rcast.u-tokyo.ac.jp/>

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 the purpose of research and development of the advanced diagnostic and therapeutic instruments for the clinical medicine and their related technologies. To date, medical engineering is not only a very important academic discipline but also 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 reform of Faculty of Medicine.

As the research field covers interdisciplinary and comprehensive researches based on the medical and engineering technique for clinical medicine, we are cooperating with various laboratories. Especially, Research Center for Advanced Science and Technology (RCAST) presided by Associate Prof. Chinzei, Department of Information Physics and Computing (IPC), Graduate School of Information Science and Technology presided by Prof. Mabuchi, and Tohoku University Biomedical Engineering Research Organization (TUBERO) presided by Prof. Imachi have been closely contacting and performing cooperative re-

searches with us.

Teaching activities

As for under-graduate education, our department takes a part in systematic lectures for the 2nd and 3rd year medical students, provides guidance and practice in the small group seminar for the 1st year medical students and in the free quarter course and other short-term course for the 3rd and 4th year medical students. In systematic lectures, basic knowledge about the advanced diagnostic and therapeutic medical engineered technologies and artificial organ technologies are presented. The basic lecture of clinical engineering is included.

As for post-graduate education, our department takes a part in series of lectures for doctor course and master course students. In the lectures, philosophy, methodology and basic and special knowledge about medical engineering 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. Especially, pre-operative management, anesthesia, surgery, post-operative management, measurement, data processing, ethical factor, and so on are learned through

the animal experiment of artificial heart. As for the subject of research, students find it by themselves from not only the field of artificial organs but also the wide area of medical engineering field. On the other hand, the education to train the leaders of biomedical engineer and clinical engineer is another important role. Other than the medical students, many students come from engineering department of our university and other university such as Waseda University and Kitasato University. Students must attend to weekly meeting. They can learn how to proceed the research work and how to report it through this meeting.

Research activities

Our research field covers artificial organs (especially artificial heart and assist circulation), biomaterials, laser surgery and medicine, thermology, measurement instruments, nerve interface, micromachine and nanomedicine, and these involved in the advanced diagnostic and therapeutic instruments and technologies.

The artificial heart (AH) study is world famous research project having a long history since 1959. Almost all the researchs such as driving mechanism, blood pump, artificial valve, materials, measurement, control method, circulatory physiology and pathophysiology have been studied. Almost all the stuffs and students join to this research. In 1995, we succeeded to survive a goat with the total artificial heart (TAH) for 532 days, which is still the longest survival record of TAH animals in the world.

To date, two main AH projects are being performed. One is the implantable TAH research and the other is the multi-institutional comprehensive project to develop a totally implantable ventricular assist device for clinical use. We invented a small blood pump with high performance, named undulation pump (UP). We are developing an undulation pump total artificial heart (UPTAH) which is the most compact implantable total artificial heart in the world. To date, we succeeded to survive a goat for 63 days with UPTAH. Using the technology of the UPTAH, 5-year project to develop a totally implantable ventricular assist device for clinical use have been performed since 2002 in cooperation with Hokkaido University, Hokkaido Tokai University, Tohoku University, Waseda University, Kyusyu University and several companies.

Physiological study 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. To date, the 1/R control is the single method to realize a physiological control of the output of TAH, in which the particular problems of TAH such as venous hypertension, slight anemia, low thyroid hormone level, and so on, are not occurred and the output is changed in accordance with metabolic condition of the animal. The 1/R control was installed in the UPTAH and the pathophysiological study is being performed.

Concerning the biomaterials, the mechanism of thrombus formation and calcification on the medical polymer surfaces, especially in artificial heart and on polymer valve have been studied. The evaluation of biocompatibility of many biomaterials is also important task.

In the field of laser surgery and medicine, the influence of various kinds of laser on tissues and organs has been studied since 1964, and laser scalpels and coagulators have been developed. The applications of laser to the minimally invasive surgery have been studied. Coronary laser angioplasty, laser revascularization of the ventricle, laser nucleotomy for lumbar disc herniation were research outcome under the cooperation with several universities and hospitals. Recently, handy type laser coagulator using a high power semiconductor laser was developed.

Thermology is one of the original works of our department in Japan. Development of instrument and basic physiological studies have been performed. Recently, imaging of effectiveness in alternative and comprehensive medicine is under the basic study.

Implantable probe for observation of microcirculation is under the development using CCD chip. This device is expected to progress the physiology of the microcirculation with the combination of the artificial heart.

Nerve interface will be very important to control the artificial organs. The basic study to develop a multiple interface array to single nerve fibers is being studied using micromachine technique.

Micromachine and nanomedicine technologies are also important for the next generation artificial organs.

Cell culture in the small hole with diameter of 100 micron and 320 micron depth was succeeded for constructing complex organ with tissue engineering technique.

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Neuroscience

1. Basic Neuroscience

Department of Neuropathology

Professor

Yasuo Ihara, M.D.

Associate Professor

Lecturer

Maho Morishima-Kawashima, Ph.D.

Associate

Satoru Funamoto, Ph.D.,

Tomohiro Miyasaka, Ph.D.

Homepage

Introduction and Organization

The Institute for Brain Research to which Department of Neuropathology originally belonged is dated back to 1935, when three laboratories were set to start brain research within the Department of Psychiatry. The first lab was headed by Dr. Teizo Ogawa, the second by Dr. Shufu Yoshimasu, and the third by Dr. Katsumi Kakeda. In 1953, the Institute for Brain Research was formally established, which consisted of six departments, namely Departments of Neuropathology, Neuroanatomy, Neurophysiology, Neurochemistry, and Psychology. In 1959, Dr. Hirotugu Shiraki promoted to the first professor of Neuopathology, followed by Drs. Tatsuya Yamamoto and Masanori Tomonaga. In 1991, Dr. Yasuo Ihara succeeded the professorship, and became the fourth professor of Neuopathology. In 1997, the Institute was closed as the Faculty of Medicine, University of Tokyo was promoted to the Graduate School of Medicine. By extensive reorganization, Department of Neuropathology now makes up the Neuroscience Division, together with Departments of Neurochemistry, Neurobiology (formerly Psychology), Neurology, Neurosurgery, and Psychiatry, and three departments from the Institute for Phonetics.

Teaching activities

As we belonged to the research institute in the past, we have not been heavily involved in the teaching activities. What we are presently involved are to provide lectures on Alzheimer's disease and neuroanatomy to premedical students, and master course students. For these five years intensive neuroanatomy course has been provided towards doctoral and master students every January for a period of seven days.

Research activities

The long-term goal of the research in our department is to determine the molecular events that lead to the development of Alzheimer's disease (AD).

Current goals include:

1 Characterization of γ -secretase—Senile plaques, one of the neuropathological hallmarks of Alzheimer's disease (AD), are composed of a small ~40-residue protein called amyloid β -protein ($A\beta$). $A\beta$ is produced from β -amyloid precursor protein (APP), through sequential cleavages by two membrane proteases referred to as β - and γ -secretases. β -Secretase is a membrane-bound as-

partyl protease, and cleaves APP in its luminal portion, generating a 99-residue-fragment called β C-terminal fragment (β CTF). β CTF in turn is cleaved by γ -secretase in the middle of its transmembrane domain, generating A β which is finally secreted into the extracellular space. While the most predominant product is A β 40, a two-residue longer species, A β 42, is believed to be the species initially deposited in the brain and predominates in senile plaques. Thus far, three causative genes for familial AD, *APP*, *presenilin (PS) 1*, and *PS2*, have been identified, and the FAD mutations found in these genes lead to increased production of A β 42, strongly suggesting that A β 42 is a real culprit for AD.

The mechanism of intramembrane cleavages at the A β 40 and A β 42 sites by γ -secretase has remained an enigma. Accumulating evidence suggests that γ -secretase is also an aspartyl protease with its catalytic site(s) sitting within the membrane. Active γ -secretase is assumed to take the form of a high-molecular-weight multiprotein complex consisting of at least four integral membrane proteins, PS, Aph-1, nicastrin, and Pen-2, all of which are essential for the emergence of full γ -secretase activity. PS1/2 appear to compose the catalytic core of γ -secretase.

γ -Secretase cleaves APP in the middle of the transmembrane domain (γ -cleavage), releasing A β , and near the membrane-cytoplasm boundary (ϵ -cleavage), producing APP intracellular domain (AICD). ϵ -Cleavage generates AICD50-99, a major product, and AICD49-99, a minor product. Although the relationship between γ - and ϵ -cleavages is still not well understood, our previous study showed that some correlations exist between the major counterparts, A β 40 vs. AICD50-99, and between the minor counterparts, A β 42 vs. AICD49-99.

We have identified several longer A β s within cells and in the brain, including A β 43, A β 45, A β 46, and A β 48. In contrast, only two species of AICD49-99 and 50-99 were identified in the newly established solubilized assay system. Thus, it is likely that β CTF undergoes first ϵ -cleavage, followed by γ -cleavages at multiple sites within its transmembrane domain. These cleavage sites are aligned on the α -helical surface of the transmembrane domain, and we speculate that β CTF is processed at every third residue from its C-terminus by γ -secretase.

2 Tau and neuronal cell death

Microtubule-binding protein tau, which promotes tubulin polymerization and stabilizes microtubules, was identified as the major component of the framework of neurofibrillary tangles (NFT) found in the brain affected by so called tauopathy, the conditions such as Alzheimer's disease (AD) and frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17). Patients affected by FTDP-17 develop execution problems, behavioral abnormalities, often parkinsonism, and finally dementia. More than 25 exonic and intronic mutations in the tau gene in FTDP-17 families are currently found, strongly suggesting that tau is directly involved in the neurodegeneration and neuronal loss.

Those animal models so far made provide both invaluable information about the nature of neurodegeneration caused by tauopathy. However, detailed pictures of neurodegeneration have remained unknown largely because of the complexity of the nervous system. We thus generated transgenic nematode expressing human WT tau or two kinds of FTDP-17 mutant tau (P301L and R406W) in six mechanosensory neurons, ALML/R, AVM, PLML/R, and PVM. They can be readily traced to their fine neuronal processes under microscopy, a condition which is difficult to obtain in other models. These neurons are characterized by distinct microtubules of a larger diameter that consist of 15 protofilaments (instead of 11), and by expression of MEC-12 and MEC-7, and distinct types of $\tilde{\alpha}$ and β -tubulin.

Decreases in the touch response are associated with various types of neuritic abnormalities. The greater these alterations are, the more the response is decreased. Various abnormal neuritic characteristics could be interpreted as derived from generation of aberrant neurites during development. These observations would suggest that dysfunction, a decrease in the touch response, is not due to neuronal loss, but may be due to the formation of abnormally generated neurites, presumably leading to the formation of abnormal neuronal circuits and resulting in null response. There appear to be two types of neurodegeneration, tau-accumulating and tau-nonaccumulating degeneration, in the affected worms. This view was previously proposed for the neocortical neurons affected by AD, based on unbiased stereological observations. Even if tau does not accu-

mulate in the cell bodies, their neuronal processes are already abnormal, suggesting that even a trace amount of tau, especially of mutant tau, can be toxic to touch neurons. We do not currently know why these two types of neurodegeneration can happen. One possibility would be that tau accumulation is a late event during the course of neurodegeneration, and the rate of accumulation varies for individual cells. In rapidly degenerating neurons, tau may not be produced sufficiently to accumulate, leading to tau-negative degeneration. In contrast, in slowly degenerating neurons, tau exists in sufficient amounts to accumulate, leading to tau-positive degeneration. This strongly suggests that tau accumulation (or formation of tau inclusions) is not required for the toxic effect of mutant tau.

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Department of Neurochemistry

Associate Professor and Head

Haruhiko Bito, M.D., Ph.D.

Assistant Professors

Hiroyuki Okuno, Ph.D.

Sayaka Takemoto-Kimura, M.D., Ph.D.

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

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 poten-

tials.

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, one postdoctoral scholar, one technical staff member, three Ph.D. and one M.S. 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 (Bitto 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), 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 synapse circuitry formation and maturation is now being scrutinized. Furthermore, we recently identified the critical lipid-modifying enzyme that controls lipid-anchoring of this kinase.

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.

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 Ca²⁺-influx while the latter was likely to be mediated at least in part by L-type voltage-gated Ca²⁺ channel activity. Thus distinct patterns and sources of Ca²⁺ influx were likely to trigger a com-

plex spatially segregated patterns of actin cytoskeletal reorganization, with variable impact on either neuronal morphology and/or synaptic protein assembly (Furuyashiki et al., PNAS, 2002).

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

What are the key signaling pathways controlling actin dynamics in central neurons? We were especially keen to resolve the contribution of the small GTPase Rho and its downstream effectors, initially in the context of developmentally regulated neuronal morphogenesis. We first established in a model cell line N1E-115 that neurite retraction was directly linked to Rho/ROCK activity (Hirose et al., J. Cell Biol., 1998). We subsequently revealed that in central neurons, in addition to its essential role in regulating growth cone motility, Rho/ROCK activity in fact acted as a negative gate that tightly controls the timing with which the first processes are initiated out from the round cell soma (Bito et al., Neuron, 2000). Disruption of Rho/ROCK activity was sufficient to immediately initiate neuritogenesis. This indicated that endogenous Rho activators, by titrating ROCK activity, continuously antagonized process/ branch formation and that local gradient of Rho activators might play a crucial role in shaping the timing and the extent of process formation (Bito, J. Biochem., 2003). Consistent with this idea, we found that in cerebellar granule cells, a chemokine SDF-1 α released from the pia mater was likely to be a predominant Rho activator via stimulation of a cognate and specific GPCR CXCR4 (Arakawa et al., J. Cell Biol., 2003). While a true gradient in SDF-1 α still remains to be demonstrated in vivo, it is intriguing to note that most active axonal process formation and elongation actually occur in the inner zone of EGL that is opposite and most distant from the interface with the pia mater (Bito, J. Biochem., 2003). Most strikingly, we demonstrated that axon elongation could actively occur in an intermediate Rho activity range that enables ROCK to be weakened enough while allowing another Rho effector mDia1 to actively mediate its effect on actin nucleation and polymerization (Arakawa et al., J. Cell Biol., 2003).

Whether similar or distinct mechanisms also operate

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

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Neuroscience

2. Speech and Cognitive Sciences

Department of Speech Science

Associate Professor

Yoshihiro Takayama, M.D.

Associate

Kenji Itoh, Ph.D.,

Michiru Makuuchi, Ph.D.

Homepage

Introduction and Organization

Speech and language are the most prominent cognitive functions distinguishing human being from non-human animals. The Department of Speech Science aims at basic, interdisciplinary studies on the human speech and language communication. The research area ranges from physical and physiological processes in speech production and perception, developmental as well as adult cognitive processes in speech and non-verbal communication to medical application of speech and hearing support technologies. Many studies are conducted in cooperation with other departments, faculties and universities such as in the field of engineering, linguistics, psychology, education and clinical neuroscience.

Teaching activities

1. Graduate Course

Speech Science and Language Communication
Pathophysiology of Higher Brain Functions
(for School of Humanities and Sociology)

2. Undergraduate Course

Introduction to Medical Data
Speech and Language Communication

* The lectures are conducted in collaboration with the Departments of Speech Physiology, Cognitive Science and Sensory and Motor Neuroscience.

Research activities

1. Brain mechanisms on spoken language production, comprehension and their linkage in human communication
2. Physical, physiological and computational modeling studies on verbal and nonverbal temporal behaviors of Japanese and others
3. Cognitive process in acquisition of native speech, language and communication skills in infants and children
4. Learning mechanisms of second language and world knowledge in adults with established first language
5. Objective and quantitative assessment of normal as well as pathological speech, language and social skills
6. Technological developments of aids for the hearing, speech, language and mentally handicapped

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Department of Speech Physiology

Associate Professor

Yoshihiro Takayama, M.D., Ph.D.

Associate

Kimihiro Nakamura, M.D., Ph.D.

Michiru Makuuchi, Ph.D.

Homepage

Introduction and Organization

The Department of Speech Physiology is one of the three departments composing the Speech and Cognitive Science Section. Research in the laboratory is currently aimed at understanding the functional architecture of the language and cognitive system.

Clinical activities

Assessment for aphasia, amnesia, apraxia, agnosia and dementia are conducted in collaboration with the Department of Neurology and the Department of Neurosurgery.

Teaching activities

1. Graduate School of Medicine
Speech Science and Language Communication.
Pathophysiology of Speech and Language Communication*.
Introduction to Neuroscience.
2. Master Course, Faculty of Medicine
Cognitive Neuroscience*
3. Graduate School of Literature
Physiology and Pathophysiology of Higher Brain Function*
4. Undergraduate School of Medicine
Speech and Language Communication*

(* Jointly organized with the Department of Cognitive Neuroscience and the Department of Speech Science)

Research activities

1. Clinical Neuropsychology:
By studying patients with disorders resulting from brain damage, we can make inferences about the kinds of cognitive representations and processes that constitute the normal system. Recent research in the field of clinical neuropsychology focused on 1. Neuropsychological sequels of acute and chronic stroke, 2. neuropsychological deficits associated with degenerative diseases, 3. short and long term neuropsychological deficits in patients with epilepsy.
2. Cognitive Psychology:
Using behavioral measures such as reaction time, answer fine-grained questions about the structure of representations and the time course of processing, we are doing studies of unimpaired individuals' performance on language tasks to reveal the ways in which the brain represents and accesses knowledge about a word's meaning, sound structure and written form.
3. Functional Neuroimaging:
We have recently begun to use functional magnetic resonance imaging (fMRI) to identify brain regions that subserve various components of language. We are performing fMRI studies to establish more appropriate description of the function of Broca's area using both language and non-language tasks.

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Neuroscience

3. Clinical Neuroscience

Department of Neuropsychiatry

Professor

Nobumasa Kato, M.D., Ph.D.

Associate Professor

Nobuo Nakayasu, M.D., Ph.D., Koichi Tsunashima, M.D., Ph.D.

Lecturer

Nagafumi Doi, M.D., Ph.D., Masatoshi Shibayama, M.D., Ph.D.,
Mieko Chinzei, M.D., Ph.D., Kiyoto Kasai, M.D., Ph.D.

Associate

Masuhiko Sakata, M.D., Tatsuo Samejima, M.D.,
Kotaro Kudo, M.D., Ph.D., Yuka Obi, M.D., Hidenori Yamasue, M.D., Ph.D.,
Yasushi Nomura, M.D.

Homepage <http://npsy.umin.ac.jp/>

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 May 2002, we have been working in the new closed ward (34 beds) and in the open ward (20 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 1200 new patients visited yearly (2005), and the total visits per year was about 35,000 (140 per day).

The secluded ward has 34 beds including 3 seclusion rooms. We also have 20 beds for psychiatric use in a general ward. Approximately 350 patients with various psychiatric disorders were admitted in a year (2005), 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 encom-

passes 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 post-traumatic stress disorder (PTSD).

Clinical Pharmacology- The atypical neuroleptics have been widely prescribed in our country. They con-

tribute 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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Department of Neurology

Professor

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

Associate Professor

Shin Kwak, M.D., Ph.D.

Lecturer

Yoshikazu Ugawwa, M.D., Ph.D.

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

Associate

Jun Shimizu, M.D.,Ph.D.,

Yasuo Terao, M.D.,Ph.D.,

Tomotaka Yamamoto, M.D.,Ph.D.,

Yaeko Ichikawa, M.D.,Ph.D.,

Yuji Takahashi, M.D.,PhD.

Homepage <http://square.umin.ac.jp/neurotky/>

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 6th 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 are putting our effort to establish excellent Institution for Neuroscience integrating basic and clinical neuroscience fields.

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 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. The molecular mechanisms of neurodegeneration in SCA17, another polyglutamine disease, were investigated. (Tsuji, S., Goto, J., Shimizu, J., Nakamura, K.,

Takahashi, Y., Momose, Y., Date, H., Iwata, A., Jin, Y., Zhou, J., , Ruberu, R.P.T., Ruberu, N.N., Suzuki, K., Nakahara, Y., Seki, N., Deoka, K.)

We have demonstrated that RNA editing of glutamate receptor subunit GluR2 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. We have been investigating to what extent the vestibular nerve stimulation is beneficial for alleviating parkinsonism and orthostatic hypotension in patients with Parkinson disease and Shy-Drager syndrome. Validity of a wearable accelerometer in evaluating anti-parkinsonism medication in outpatient clinic has been also under investigation. (Kwak S., Kawahara. Y., Sun, H., Pan, W.D., Hideyama, T., Nishimoto, Y., Ito, K.)

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. 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 mechanisms for DBS in the patients. We have also recently developed a new, highly effective TMS method to induce a 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. (Ugawa, Y., Terao, Y., Hanajima, R., Okabe, S., Arai, N., Terada, S., Yugeta, A., Hamada, M., Furubayashi, T., Mizuno, Y., Shirasawa, H., Machii, K.)

In the field of neuromuscular diseases, we provide diagnosis of neuromuscular pathology (muscle and nerve biopsies) and autoantibody testing. Our neuromuscular pathology service evaluates approximately 100 neuromuscular biopsy specimens each year. In research field, we focus on exploring the mechanism of inflammatory myopathies and immune mediated neuropathies. We also focus on establishing improved methods of diagnosis and treatment of these diseases. Using clinical, pathological and molecular techniques,

we aim to increase understanding of the etiology and pathogenesis of neuromuscular diseases. (Shimizu, J., Kowa, H., Mikata, T., Sugimoto, I., Kano, S., Uchinokura, A., Tokimura, N., Tajiri, M., Mashiko, R.)

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Department of Neurosurgery

Professor

Nobuhito Saito, M.D., Ph.D.

Associate Professor

Akio Morita, M.D., Ph.D.,

Nobutaka Kawahara, M.D., Ph.D.

Lecturer

Tomoki Todo, M.D., Ph.D.,

Kensuke Kawai, M.D., Ph.D.,

Yasushi Ino, M.D., Ph.D.

Associate

Akira Iijima, M.D.,

Kyosuke Kamata, M.D., Ph.D.,

Jyunichi Tanaka, M.D.,

Minoru Tanaka, M.D., Ph.D.,

Shigeo Sora, M.D.,

Hirofumi Nakatani, M.D., Ph.D.,

Keisuke Maruyama, M.D., Ph.D.,

Keisuke Takai, M.D.

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

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 2004 through March 2005, 12263 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 2004 and 2005, 567 and 600 patients were admitted to the Neurosurgical Ward, respectively. Three hundred and forty eight and 322 surgical procedures were performed with 126 and 140 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 4000 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 accept 5 residents in 2006 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.

tals.

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 "tailor-made" chemotherapy

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) Translational research with Department of Engineering

We have developed Slave-Master type microsurgical robotic system in our medico-engineering laboratory. The prototype of our system enabled micro-anastomosis of very fine arteries in the depth of 12cm. Also, our system showed very steep learning curve in performing micro-procedures. The prototype system was demonstrated at EXPO 2005 in Aichi in June 2005, and our basic result has been presented in international meetings and published in following journals.

In the other project, we are developing new drug delivery system, which can be effectively concentrated to the malignant brain tumors and deliver effective therapeutic agents.

4) 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. 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.

5) 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 pre-surgical 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. The electrophysiological monitoring such as electrical cortical and subcortical stimulations, and direct recording of the cortical potentials are simultaneously performed to develop highly reliable non-invasive techniques of the functional brain mapping, validating the combined results. This clinical research gives favorable potentials to preserve the eloquent brain functions and improve the patients' quality of life.

6) Prospective National registry of Unruptured Cerebral Aneurysms: Unruptured Cerebral Aneurysm Study In Japan (UCAS Japan)

Since 2001, UCAS Japan has been conducted in our department. This is a national study to identify 1) natural course of unruptured cerebral aneurysms in Japanese population and 2) risks associated with management of unruptured aneurysm in Japanese institutions. Currently we enrolled more than 7000 patients with unruptured cerebral aneurysm found in 404 institutions and prospective follow-up has been conducted using on-line registry system. Since January 2006, UCAS II; prospective Quality of Life analysis of patients with unruptured cerebral aneurysms has also been started.

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Social Medicine

1. Occupational, Environmental and Preventive Medicine

Department of Molecular Preventive Medicine

Professor

Kouji Matsushima, M.D., Ph.D.

Associate Professor

Sho Ishikawa, M.D., Ph.D.

Associate

Shinichi Hashimoto, Ph.D.,

Nobuyuki Yamazaki,

Makoto Haino, M.D., Ph.D.

Takeshi Shimaoka, Ph.D.

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

Introduction and Organization

The Department of Molecular Preventive Medicine was established in 1885. It was designed to offer both a high level of hygienic education and facilities for specialized research. At present, it is our responsibility to give lectures, seminars and courses for experiments and practical training on the preventive medicine to the third grade medical students. The professor, several invited lecturers (including adjunct staffs) and four 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 grade medical students. The course is consisted of lectures, seminars, experiments, and practical training are provided by our

own staffs and also by the experts outside: National Institute of Infectious Diseases (Dr. Takebe), Yamana-shi University (Dr. Matsugo), Mie University (Dr. Kawanishi), 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 and dendritic cells in vivo in various animal disease models.
- 2) Molecular analysis of chemokine receptor signaling pathway.
- 3) Serial analysis of gene expression in 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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Department of Public Health

Professor

Yasuki Kobayashi, M.D., Ph.D.

Associate Professor

Kazuo Inoue, M.D., Ph.D.

Lecturer

Hajime Sato, M.D., M.P.H., Ph.D., D.P.H.

Associate

Satoshi Toyokawa, Ph.D.

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

Introduction and Organization

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.

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 Medical Sciences (MSc), and Doctor of Medical Sciences (equivalent to Ph.D.).

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) Graduate 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.

Part of the seminars described above has been formally open to all students in the Graduate School of Medicine as an intensive practice course on study methods in public health. At the same time, the Department has provided the students enrolling in the Master of Medical Science program with a short course on public health.

2) Undergraduate Program

In the winter term of the second year in the School of Medicine (M2), students are provided with the following lectures: (1) current issues in the field of public health, (2) preventive services, (3) epidemiology, (4)

health economics, (5) community health (6) occupational and environmental health, (7) infection and tuberculosis control, (8) behavioral medicine, (9) international health, and (10) health policy in Japan. Similarly, in the fourth year (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.

Field practice and laboratory work in public health is due in the spring term of 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 (a faculty member or part-time lecturer). Each group conducts field practice, review work, or laboratory work and writes a report in the style of original or review paper. The reports submitted are bound and made available to those students in subsequent years.

The Department also provides those lectures related to public health and occupational medicine for undergraduate students in the School of Health Sciences and Nursing, and the Faculty of Engineering.

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 supply and demand sides 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 from international comparative perspectives, especially tobacco smoking control, and patient isolation policy for Hansen's disease. These studies have been published in some international policy journals. Recently, we started 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 tackled the issues of health effects of lead and other heavy metals and solvents, and health effects of pesticides in developing countries as part of the Alliance for Global Sustainability project. We have also been interested in epidemiology and prevention of life-style diseases and mental problems among workers in various occupational settings.

3) Community and clinical epidemiology

We have done several epidemiological studies in community, such as active life expectancy for the community elderly, as well as those studies in clinical epidemiology. Most of these studies have been carried on in collaboration with local communities or clinical departments.

In relation to the above activities, two events should be noted: (1) Dr. Kazuo Inoue hosted the 9th Academic Meeting of Emergency Medicine for Rural Areas and Remote Islands in 2005, and (2) Dr. Hajime Sato was awarded the 2005 Walter Beach Award jointly by the Policy Study Organization (Washington D.C.) and the Southern Political Science Association (Georgia) in the United States.

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Department of Radiological Health

Associate

Akinori Morita, Ph.D.

Homepage <http://plaza.umin.ac.jp/~uthouki/index.html>

Introduction and Organization

The Department of Radiological Health was originally established in 1961 as a joint department of university's central institution for education & research of peaceful use of atomic energy. The research fields of this department are fundamental and applied radiological protection and safety. After the retirement of Professor Yoshiro Aoki, Professor Norio Suzuki of the Department of Radiation Oncology concurrently held the professorship of the Department from 2000 to his retirement in March 2003. Since 2000, the Department has been in collaboration with the Department of Radiation Oncology at the same working place. In April 2003, Department of Radiation Oncology and Radiation Research Institute were integrated into Section of Radiation Biology as a division of *Center for Disease Biology and Integrative Medicine*. Thus, the Department of Radiological Health is now in collaboration with the Section of Radiation Biology.

Teaching activities

Education for the second- and forth-year medical students was provided as courses of the biological effects of radiation, the radiological protection and the radiological health. Each course consisted of lectures and experiments, through which the students learned the concept of radiological protection and the practical techniques of radiological safety for workers and clinical patients. The third-year students of health science course were also provided with a course of radiation hygiene, which consisted of lectures and experiments. The students learned the concepts of radiological protection, techniques of risk assessments of radiation and

practical technique of radiation safety for workers and the public. The students learned the concepts of radiation safety and hygiene for vocational and medical use. The department provided the special lectures on the radioecology, the environmental radiation risk assessment and radiological protection for post-graduated students. After the retirement of Professor Suzuki, the Section of Radiation Biology has covered these teaching activities.

Research activities

The experimental researches in the Department had covered many fields such as biological effects, risk assessment, computer simulation of biological effects and bio-kinetics, and risk management. The main focuses of research activities had been the following categories;

- 1) Radiological protection for patients and workers in medical field.
- 2) Risk assessment and risk perception of low dose radiation.
- 3) Radiation-induced carcinogenesis.
- 4) The combined effects of radiation and chemical agents on embryos/fetuses.
- 5) Bio-kinetics of radionuclides in fetus body and dose estimation of internal exposure to fetuses.
- 6) The embryonic and fetal effects of non-ionizing radiation.
- 7) Estimation of body compositions with whole body gamma counter.
- 8) Medical emergency plans for workers in nuclear accidents.
- 9) Means of health care for victims of atomic explosions in Hiroshima and Nagasaki.
- 10) The methods of health control of workers of nu-

clear power plants.

Current research activities are focused on development of a new method of radiation protection based on regulation of p53.

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Social Medicine

2. Forensic Medicine, and Medical Informatics and Economics

Department of Forensic Medicine

Professor

Ken-ichi Yoshida, M.D., Ph.D.

Lecturer

Koichi Uemura, M.D., Ph.D.

Associate

Kaori Shintani, Ph.D.,

Kou Takahashi, M.D, Ph.D.

Homepage <http://plaza.umin.ac.jp/~forensic/>

Introduction and Organization

Our department was founded as the first department of forensic medicine in Japan in 1888. Actually Associate Professor Kuniyoshi Katayama had already lectured in “judicial medicine” to students in University of Tokyo in 1882. Professor Katayama insisted that they should merely study judicial medicine as well as trial relations in depth on the legislation, so he renamed “judicial medicine” to “forensic medicine” in 1891. Professor Katayama was the first professor in our department, and he held additional post of neuropsychiatry professor.

Professor Sadanori Mita was famous as a serologist, and he was founded the serological department (the department of Immunology) in University of Tokyo. He discovered the antigen-antibody reaction and complement fixation reaction.

Professor Tanemoto Furuhashi was the first person of an ABO blood group system study, and he contributed the development of criminology. He autopsied some cases to be left in criminology, too.

Professor Shokichi Ueno studied serology, he was discovered the complex III. In the time of Professor Ueno, the first national detective examiner class was performed.

In the time of Professor Toshiyuki Miki, he was not able to autopsy for University of Tokyo dispute for four years. However, he left many achievements in a study

of a blood type and performed a paternity test.

Professor Ikuo Ishiyama contributed to forensic pathology. He introduced DNA fingerprint and PCR technique into forensic medicine.

Professor Takehiko Takatori studied the formation of adipocere biochemically. He dissected the sarin subway attacks in Tokyo and specified the cause of death was sarin.(?)

Now Professor Ken-ichi Yoshida studied the cause of death investigation system of a medical malpractice, a dissection system as well as heart-related sudden death. He performs a medical care-related death model trial from 2005.

The staff of our department consists of one professor, one lecturer, two associate, one special technician, one technician, five postgraduate students and one researcher.

Forensic autopsy

The determination of precise cause of death is the most important work in our department. So we autopsy 80-90 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, drinking, toxicological and blood type testing of each case, too. Finally, forensic pathologists in our depart-

ment diagnose the cause of death. Official documents written in our forensic judgments are so precious that we keep them since first autopsy case in 1889. We have serious responsibility in the determination of cause of death.

Recently, we are often confronted with various problems such as medical accidents and malpractice.

In our department, we provide detective examiners opportunities to learn forensic autopsy, they will conduct on the first line of crime investigation in Japan.

Teaching activities

As for under-graduate education, our department takes a part in systemic lectures for the 6th year medical students, Free Quarter training course for the 3-4th year medical students, and Clinical Clerkship learning for the 5th year medical students.

In systemic lectures, comprehensive presentation for the understanding of basic knowledge about the forensic medicine, the detail exposition of forensic cases is performed.

Clinical clerkship at the 5th year of the educational program is the early exposure to the forensic practice, several lectures about body phenomenon, injury, asphyxia, internal sudden death, disturbance from abnormal circumstances, poisoning, forensic odontology, object inspection and forensic training are provided for a relatively long period (for one month). In Free Quarter training course for the 3-4th year medical students, they have opportunities to experience forensic duty works for 2 weeks.

Research activities

Our research is wide ranged from social issues to molecular biology. Main research interest in our department is as follows:

- 1) More than two thirds of the causes of unusual death are ischemic heart disease. Psychic stress from accidents, assaults, overwork and physical restriction often trigger off these deaths.
So our laboratory specializes in myocardial and nerve cell disorders after ischemia, and the roles of molecular mechanism of cell death. We also study differences of cell response, change of cytoskeleton after ischemia or stress
- 2) Forensic practices are associated with various legal or social problems of medicine, and so our doctor course students who graduated from the faculty of law conduct attitude surveys of "unusual death", information disclosure after autopsy on the legal and social issues associated with medical acts.

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tions for the dispersal of Northeast Asians. *Microbes Infect* 2004 6: 596-603.

Department of Medical Informatics and Economics

Professor

Kazuhiko Ohe, M.D.,Ph.D.

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

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 post 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 ex-

isted 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. T. Imamura and Lecturer. K. Miyo from DPIM, Prof. T. Kiuchi from UMIN center, Visiting assoc. prof. S. Oku from the Department of Healthcare Related Informatics that is the affiliated department (April 2004 -), Visiting assoc. Prof. H. Hashimoto from the Department of Health Management and Policy that is also the affiliated department (Oct. 2005 -), Assoc. Prof. R. Yamamoto from Interfaculty Initiative in Information Studies, Graduate School of Interdisciplinary Information Studies, and Prof. H. Oyama and Assoc. Prof. Y. Onogi from Division of Clinical and Bioinformatics Engineering, Department of Clinical Bioinformatics, Graduate School of Medicine.

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. 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 post.

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. The purpose of this course is to foster research and technical professionals who did not graduate from 6-year undergraduate program but has wishes to take the doctoral course of Medical Science in the university of Tokyo. It is required for students in the master's course of Medical

Science to pass the interview examination in order to enroll the doctoral course.

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 FY2004 are seven in doctor's course for Medical Informatics and Economics, two in master's course for Health Informatics, and two in master's course for Medical Science. The students in FY2005 are six in doctor's course for Medical Informatics and Economics, one in doctor's course of Health Informatics, one in master's course of Health Informatics, and one for master's course of Medical Science.

The students' researches cover various topics. The main ones are the analysis of medical cost for the DPC Classification", development of method for mapping Japanese standard terminology of disease Names to English SNOMED-CT, a study on the Reference Functional Model for standard EHR systems, a study on the communication model for healthcare institution, a study on methods for healthcare safety control, and medical support by electronic description format of chemical therapy regimen and inference mechanism.

Research activities

Our main research domains are 1) application studies on developments of clinical information systems as typified by hospital information system and electronic health records system, 2) studies on medical safety control 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, 8) application of virtual environment for healthcare.

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

- 1) The development of information model of basic functions required for Standardized Electronic Health Records (EHR) Systems (Research on Health Technology Assessment H15-IRYOU-046 from Health and Labour Sciences Research Grants, 2003-2004)

This research surveys the required functions for EHR systems. Based on the survey result, the functional model for standard EHR systems is constructed. The standardization of function provided by various EHR systems is expected to be promoted.

- 2) A study on satisfaction of medical information needs and the protection of personal information in EHR (Grant-in-Aid for Scientific Research on Priority Areas (2) No.16016227 from Ministry of Education, Culture, Sports, Science and Technology, 2003-2005)

In the age that EHR is widely used, it will increase the possibility that clinical information in EHR may be accessed and referred by more clinical staffs than that in paper-base health records. Although it has some advantages, the disadvantage that clinical information is accessed by the staff that has no need to refer the information exists. This research discusses how to control the unnecessary access by analyzing system log.

- 3) A study on development methods for large scale ontology databases of medical terms and concepts (Grant-in-Aid for Scientific Research (A)(2) No.16200039 from Ministry of Education, Culture, Sports, Science and Technology, 2004-2007)

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 described in 6).

- 4) A study on a bedside system for automatic security surveillance (H16-IRYOU-026 from Research on Health Technology Assessment, Health and Labour Sciences Research Grants, 2004-2006)

Existing bedside system for security control is just checking the barcodes or IC tags of medical prod-

ucts, patients and staffs. This control depends on conscious and active acts of staffs. This research, however, develops a method to achieve automatic detection of approaching objects by applying various information engineering methods. It is expected that the mix ups of objects are prevented before they occur.

- 5) A study on the development of a patient-oriented, event-driven, and intellectual clinical support subsystem (Industry – academia - government collaboration project with Fujitsu Limited, 2004-2008)
- 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.

- 6) Construction of Clinical and Medical Ontology Database (Industry – academia - government collaboration project with the Japan Anatomy Laboratory, Co, Ltd., 2004-2008)

This research aims the construction of actually available clinical and medical ontology with approximately 200,000 terms. It also develops application tools for the ontology.

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Internal Medicine

1. Medicine I

Department of Cardiovascular Medicine

Professor

Ryozo Nagai, M.D., Ph.D.

Associate Professor

Yasunobu Hirata, M.D., Ph.D.

Lecturer

Yoshinori Seko, M.D., Ph.D.,

Hiroshi Yamashita, M.D., Ph.D.

Hospital Lecturer

Nobukazu Ishizaka, Ph.D.,

Koji Maemura, Ph.D.

Homepage <http://plaza.umin.ac.jp/~utok-card/>

Introduction and Organization

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

Outline of department

Staff: one professor (Ryozo Nagai), 1 associate professor (Yasunobu Hirata), 2 assistant professors (outpatient clinic Yoshinori Seko and hospital ward Hiroshi Yamashita), 15 research associates, 9 staff members, 30 graduate school students, 6 researchers, 1 members on leave and 2 members studying abroad.

Clinical activities

In 2004, 1,107 patients were admitted to our hospital ward of which 80% were due to ischemic heart disease. Diagnostic tests reached large numbers including about 7,000 echocardiography exams, 1,500 Holter 24-hour electrocardiogram exams and 1,300 treadmill exams. Cardiovascular angiograms were conducted in 1,450 patients, of which 491 cases received coronary angioplasty. Other interventional procedures such as catheter ablation were also performed frequently (catheter ablation 31, pacemaker implantation 56). There are about 50 beds for our division in the hospital ward. The bed occupancy rate is 95%. Duration of hospitalization is shortest among departments at an average of 13.0 days.

Out-patient clinics are available as part of the De-

partment of Medicine or as a specialized department. Patient numbers are increasing each year to 43,612 in 2004. 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 160 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 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. Immunological basis of myocarditis and dilated cardiomyopathy
14. Anti-arrhythmia therapy using catheter ablation
15. New treatment for pulmonary hypertension
16. Development of drug eluting stent
17. Clinical application of vasoactive substances for cardiorenal insufficiency
18. Bone marrow-derived cells in atherosclerosis
19. Regeneration therapy for cardiovascular disease

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Department of Respiratory Medicine

Professor

Takahide Nagase, M.D., Ph.D.

Associate Professor

Hajime Takizawa, M.D., Ph.D.

Lecturer

Nobuya Ohishi, M.D., Ph.D.

Associate

Taiji Nagata, M.D., Ph.D.,

Masashi Desaki, M.D., Ph.D.,

Taisuke Jo, M.D., Ph.D.,

Hiroshi Kitagawa, M.D., Ph.D.

Tadashi Kohyama, M.D., Ph.D.,

Hidehiko Mizuguchi, M.D.,

Hiroyuki Takahashi, M.D., Ph.D.,

Homepage <http://kokyuki.umin.jp/>

Introduction and Organization

The staff of the Department of the Respiratory Medicine, Graduate School of Medicine, University of Tokyo, consists of 1 professor, 1 associate professor, 1 lecturer, and 7 assistant professors. In the University of Tokyo, affiliated hospitals and foreign institutions, approximately 50 members belong to the Department. In the University of Tokyo Hospital, 20 respiratory physicians are doing clinical works.

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

Based on the fact that a number of patients with respiratory diseases including lung cancer and COPD is tremendously increasing, fruitful results of respiratory research 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, asthma and COPD. Especially, we

have been intensively studying the molecular mechanisms underlying the pathogenesis of lung disorders. Our research goal is to develop novel therapeutic tools to manage these pulmonary diseases.

Clinical Activities

The Department of Respiratory Medicine is responsible for the out-patient care as well as the diagnosis and treatment of in-patients (40 cases on average). 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, pneumonia, chronic obstructive pulmonary disease (COPD), interstitial lung diseases, asthma, and other respiratory failure. Our department contributes to the pre- and post-operational evaluation of respiratory functions, and also receives consultation from other departments.

In respiratory diseases, there are several disorders to which no pharmaceutical agents are currently effective.

For example, acute respiratory distress syndrome (ARDS) is an acute lung injury and the mortality rate for ARDS is extremely high despite of intensive care using currently available drugs. Idiopathic pulmonary fibrosis (IPF) is a progressive and fatal disorder of the lung parenchyma, while no useful drugs are currently available to treat IPF. However, their mechanisms still remain to be elucidated. We would like to make every effort to develop a novel and potential therapeutic approach to these diseases.

Number of in-patients in 2004

1. Lung cancer	221
2. Respiratory infection	60
3. COPD	41
4. Interstitial pneumonia	33
5. Malignancy (except for lung cancer)	24

A weekly chart round and professor's round are scheduled for Tuesday afternoon. A specialized clinical conference is held, together with respiratory surgeons and radiologists, where radiographic diagnosis, indication of thoracoscopic biopsy, CT-guided biopsy, and surgical and radiological treatment are discussed.

Teaching Activities

As for under-graduate education, our department takes part in systemic lectures and specific learning for diagnosis 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 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 points for planning the diagnosis and treatment in collaboration with the Faculty of the Department of Respiratory Surgery.

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. Several lectures about the specific topics important in respiratory medicine such as fundamental chest radiology, treatment of asthma and COPD, and oxygen therapy are provided by the respiratory specialists.

Clinical clerkship at the 5th year of the educational program is actively performed to facilitate the early exposure to the clinical practice for a relatively long period (for one month), and, in general, is very highly appreciated by the students.

As for the post-graduate education, 7 to 8 junior residents join the Department of General Medicine on the 13th floor simultaneously for one month, 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, asthma, COPD, diffuse panbronchiolitis (DPB), interstitial lung diseases, pulmonary vascular diseases and others. We have also been studying the effects of air pollutants such as diesel exhausts. Epidemiological, clinical, cellular and molecular techniques are utilized for the elucidation of novel findings in respiratory medicine. Postgraduate students as well as the Faculty members make considerable studies about chemokines/cytokines, prostanoids, airway epithelial cells, smooth muscle cells and eosinophils. Genetic studies about asthma, diffuse panbronchiolitis, and lung cancer have also been fruitful. These results have been presented and/or published in the Scientific Meeting and/or peer-review Journals. Our main research projects are as follows.

Clinical studies of lung cancer, COPD, bronchial asthma and pulmonary fibrosis

Epidemiological studies of diffuse panbronchiolitis (DPB) and interstitial lung disease

Molecular mechanisms underlying the pathogenesis of acute lung injury or ARDS

Molecular mechanisms underlying the pathogenesis of pulmonary fibrosis

Analysis of disease models using genetically- engineered mice

Effects of air pollutants such as diesel exhausts on airway hyperresponsiveness Roles of chemokines/ cytokines and eicosanoids on airway epithelial cells, smooth muscle cells and eosinophils.

DNA methylation and lung cancer

Establishment of conditional vectors for hairpin siRNA knockdowns

Establishment of CpG island searcher

Hajime Takizawa is an Associate Editor of American Journal of Respiratory Cell and Molecular Biology, an official Journal of American Thoracic Society. Takahide Nagase is an Associate Editor of Respiriology and an Editorial Board Member of American Journal of Physiology.

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Department of Gastroenterology

Professor

Masao Omata, M.D., Ph.D.

Lecturer

Haruhiko Yoshida, M.D., Ph.D.

Minoru Tada, M.D., Ph.D.

Shuichiro Shiina, M.D., Ph.D.

Associate

Hiroshi Kanamori, M.D., Ph.D.

Hiroshi Mitsui, M.D., Ph.D.

Hirosato Mashima, M.D., Ph.D.

Keiji Ogura, M.D., Ph.D.

Mikio Yanase, M.D., Ph.D.

Hajime Fujie, M.D., Ph.D.

Hideo Yoshida, M.D., Ph.D.

Naoki Sasahira, M.D., Ph.D.

Tomoaki Tomiya, M.D., Ph.D.

Naoya Kato, M.D., Ph.D.

Makoto Okamoto, M.D., Ph.D.

Yutaka Yamaji, M.D., Ph.D.

Goichi Togo, M.D., Ph.D.

Hiroyuki Isayama, M.D., Ph.D.

Mitsuhiro Fujishiro, M.D., Ph.D.

Ryosuke Tateishi, M.D., Ph.D.

Homepage <http://www.h.u-tokyo.ac.jp/gastro/>

Introduction and Organization

The Department of Gastroenterology was established through the reorganization of the Postgraduate School of Medicine and that of the Division of Internal Medicine of the University of Tokyo Hospital in 1998. It is now constituted of a professor, three lecturers, sixteen associates, six fellows, fifty graduates including five students from abroad, and several other visiting members. The north and south wings on the 11th floor of Ward A provide core hospital rooms for the department. The department is responsible for both medical practice and education on gastroenterology.

Clinical Activities

The Department of Gastroenterology is in charge of about ninety inpatients on average. We receive about 40 new patients each week, with an average hospital stay of 16 days. A resident, a junior and a senior staff members bear the responsibility for the medical man-

agement of each inpatient, in collaboration with concerned subspecialty groups. In addition, the staff members examine about 4,700 outpatients with various digestive diseases in a month. Professor's ward round is performed on Monday and Wednesday mornings and specialty and subspecialty clinical conferences are held on Monday evening.

The most frequent cause of admission is hepatocellular carcinoma (1,000 patients a year). Eighty % of patients with hepatocellular carcinoma receive medical treatment; percutaneous radiofrequency ablation. We also perform radiofrequency ablation for metastatic liver tumors. ERCP is performed on 650 patients each year. Patients treated for choledocholithiasis with endoscopic papillary balloon dilation method exceeds 1,000, possibly the largest in the world. Internal endoscopic metallic stent is preferred to percutaneous external drainage in the palliative care of malignant obstructive jaundice (100 patients a year). ESD (endoscopic submucosal dissection) is performed as curative endoscopic treatment for neoplasms in the stomach or

colon (210 patients a year) and endoscopic variceal ligation for esophageal varices (50 patients a year) are also frequently done. We recently introduced double-balloon endoscopy for thorough examination of the small intestines. All those interventions are performed by members of the department especially trained in each technique.

On outpatient basis, ultrasonography is performed on 12,000 patients, gastroduodenal endoscopy on 5,000 patients and colonoscopy on 2,800 patients each year. About 200 cases of gastric cancer and 100 of colorectal cancer are detected annually and about 40 % of them are treated endoscopically.

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 an inpatient and joins the group of physicians in charge of the patient in medical examination and treatment. The results are to be reported to the professor at the end of the course. Students are also requested to be present at the weekly round by the professor, various gastroenterological examinations and treatments, and educational lectures on gastroenterology given by staff members. They also read and summarize gastroenterological articles on top-notch 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 medicine. Presentation at scientific meetings 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 educating residents. The majority of them also start medical researches, basic or clinical, as a graduate student. Currently, we have 50 students who were graduated from more than 30 medical schools in Japan.

Research Activities

Since gastroenterology covers various organs, everything below the diaphragms except for the kidneys and the reproductive system, and protean diseases, such as neoplasm, infection, metabolic disorders and mechanical ones, themes of research are virtually unlimited, as shown in the list of publication described below. Basic and clinical researches are equally encouraged, on condition that the results may eventually benefit the cure of patients with gastroenterological disorders. In 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 vitamin K or interferon to prevent recurrence of hepatocellular carcinoma, evaluation of diagnostic usefulness of angiography during computed tomography, and radiofrequency ablation for liver metastasis of colorectal cancer. We have also designed clinical trials for TSU-68 for advanced hepatocellular carcinoma, erythropoietin for anemia introduced by interferon plus ribavirin therapy, TS-1 alone or plus gemcitabine for pancreatic and bile duct cancers.

The department of gastroenterology is dedicated to pursuing better medicine, for which exclusively these researches, basic or clinical, are conducted.

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Internal Medicine

2. Medicine II

Department of Nephrology and Endocrinology

Professor

Toshiro Fujita, M.D., Ph.D.

Associate Professor

Tomoki Okazaki, M.D., Ph.D.,
Keiichi Hishikawa, M.D., Ph.D.,
Takanari Gotoda, M.D., Ph.D.,

Katsuyuki Ando, M.D., Ph.D.,
Shinya Kaname, M.D., Ph.D.,
Yoshio Uehara, M.D., Ph.D.

Lecturer

Shu Uwatoko, M.D., Ph.D.,
George Seki, M.D., Ph.D.,
Tatsuo Shimosawa, M.D., Ph.D.,
Taroh Iiri, M.D., Ph.D.,
Masaomi Nangaku, M.D., Ph.D.

Seiji Fukumoto, M.D., Ph.D.,
Eisei Noiri, M.D., Ph.D.,
Hideyuki Negoro, M.D., Ph.D.,
Koji Takano, M.D., Ph.D.,

Associate

Toshihiro Okuda, M.D., Ph.D.,
Etsu Suzuki, M.D., Ph.D.,
Masashi Isshiki, M.D., Ph.D.,
Takeshi Marumo, M.D., Ph.D.,
Yugo Shibagaki, M.D., Ph.D.,
Junichi Hirahashi, M.D., Ph.D.,
Hideomi Yamada, M.D., Ph.D.,

Akihiro Tojo, M.D., Ph.D.,
Katsutoshi Takahashi, M.D., Ph.D.,
Shigeyoshi Oba, M.D., Ph.D.,
Miki Nagase, M.D., Ph.D.,
Noriko Makita, M.D., Ph.D.,
Yuichi Hori, M.D., Ph.D.,
Yoshitaka Ishibashi, M.D., Ph.D.

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

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. We have 18 beds on the 12th floor of the Northern Ward of the Tokyo University Hospital, and ten beds for hemodialysis. Usually we have up to 30 in-patients 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 and Teaching 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. Particular cases are further discussed with guest specialists from outside 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 gland, adrenal glands and genital 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 water and mineral metabolism disorders.

Research activities

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.

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(Total 139 publications)

Department of Metabolic Diseases

Professor

Takashi Kadowaki, M.D., Ph.D.

Lecturer

Yoshiyasu Kaneko, M.D., Ph.D.,

Kazuyuki Tobe, M.D., Ph.D.

Associate

Kazuhisa Tsukamoto, M.D., Ph.D.,

Jun-ichi Osuga, M.D., Ph.D.

Ken Ohashi, M.D., Ph.D.,

Kazuo Hara, M.D., Ph.D.

Masumi Hara, M.D. Ph.D.,

Hideyuki Sakoda, M.D., Ph.D.

Midori Fujishiro, M.D., Ph.D.,

Mitsuru Ohsugi, M.D., Ph.D.

Homepage <http://dm.umin.jp/>

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 of diseased organs. The physicians specialized in the metabolic diseases from 3 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 the present Professor Dr. Takashi Kadowaki (2003-present), we have provided a wide-ranged clinical, teaching and research activities. Currently, we hold 35 beds mainly on the 12th floor of the Inpatient Ward of the Tokyo University Hospital, and take care of more than 30 patients constantly. Besides the staffs listed above, our division holds faculties in branches, for example, 21st Century COE Program (associate professor, Dr. Kohjiro Ueki), Department of Integrated Molecular Science on Metabolic Diseases

(associate professor, Dr. Toshimasa Yamauchi), and Department of Clinical Bioinformatics. With all these staffs, we intensively instruct and teach the residents and under-graduate 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 25 students of Graduate School in our division. With all these members, we vigorously 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 superior and warm-hearted medicine to each patient. We have outpatient clinics from Monday through Friday, and take care of more than 4000 patients. In the inpatient care unit, 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, hyperlipidemia and obesity are very popular in Japan, and cause 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 lectures to the patients every day in the inpatient ward, and also give lectures once a week in the outpatient unit. In addition, in collaboration with co-medical staffs of our hospital, we provide patients well-reasoned instructions regarding diet therapy, excise therapy and medication therapy.

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

Teaching activities

As for under-graduate 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 make a medical interview, check physical findings and make the actual plans for the diagnosis and treatment. Several lectures that lead to profound understandings of the metabolic diseases are provided by the staffs.

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 others 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 studying molecular mechanisms of type 2 diabetes and its susceptibility genes. By using gene targeting, we have been investigating the role of insulin signal transduction in the development of diabetes. We are also studying the molecular mechanisms by which obesity and hypertrophic adipocytes cause insulin resistance. We are trying to elucidate the mechanisms by which adipose-tissue-derived factors, adipokines, contribute to the development of the insulin resistance and metabolic syndrome, and also to explore the signal transduction pathways of major adipokines including adiponectin/AdipoR, MCP-1, resistin and RELM.

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 have been trying to elucidate the pathogenesis 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

We study 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 biology technique, we are analyzing the roles of lipid transporters, enzymes, nuclear receptors and the anti-oxidative proteins on the lipid disorders and atherosclerosis. At present, we are interested in the cholesterol and lipid absorption from the intestine and lipid handling in the cells.

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Department of Hematology and Oncology

Professor

Mineo Kurokawa, M.D., Ph.D.

Lecturer

Toru Motokura, M.D.,

Yoshinobu Kanda, M.D., Ph.D.

Special Lecturer (Hospital)

Akira Hagaishi, M.D., Ph.D.

Associate

Koji Izutsu, M.D., Ph.D.,

Takashi Asai, M.D., Ph.D.

Takuro Watanabe, M.D.,

Hiroyuki Sato, M.D., Ph.D.

Homepage

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 and graduate students. These activities are performed by the united efforts of all members who belong to the department. As of March in 2006, the staff of Department of Hematology and Oncology consists of thirty-nine members including one professor, 2 lecturers, one special lecturer (hospital), and 4 associates.

Clinical activities

On average, 60 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. 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 hamatopoietic stem cell transplantation in the treatment of hematological disorders.

Approximately 90 patients with acute leukemia, 100 with malignant lymphoma, 25 with chronic leukemia, 15 with multiple myeloma, 20 with myelodysplastic syndrome, and 60 with the other diseases are annually admitted to our ward. Out-patient clinical services are provided daily in the morning and afternoon using three booths. One of our final goals in the clinical activities is to cure all patients with hematological malignancies.

Here are some technical aspects on the treatment

strategy:

1. 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.
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. Several clinical studies with allogeneic stem cell transplantation have been also conducted. These include RIST for pancreatic cancer, transplantation from a donor with mismatched HLA at two loci or more. All these studies are approved by the ethical committee of the Faculty of Medicine.

Teaching activities

A lecture course on etiology, pathogenesis, clinical and laboratory features, differential diagnosis, therapy and prognosis for all hematological diseases is provided for the second grade medical students. The course contents include:

1. Mechanisms of hematopoiesis, transplantation medicine and cell therapy
2. Acute leukemia and myeloproliferative disorders
3. Bone marrow failure syndrome (aplastic anemia and myelodysplastic syndrome)
4. Lymphoma and myeloma
5. Hemostasis and thrombosis
6. Hemolytic anemia and anemia of various causes.

Courses for bedside learning on diagnostic and therapeutic issues and arts are given for the third grade

medical students on a man-to-man basis with a senior faculty member that are erudite both in general internal medicine and in hematology and oncology. During the one-week case-oriented course, students learn the basic techniques of medical interview and physical examination, interpretation of laboratory tests, and practical medical procedures.

Research activities

The major research projects are focused on molecular mechanisms of hematopoietic tumors, hematopoietic transcription factors, signal transduction mechanisms in hematopoietic cells, chromosomal and genomic approaches to leukemogenesis, generation of murine models for leukemias, proliferation and differentiation of hematopoietic stem cells, and development of immunotherapy for hematopoietic tumors. 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 two years are listed in the reference.

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Department of Allergy and Rheumatology

Professor

Kazuhiko Yamamoto, M.D. (Rheumatology, Allergology)

Lecturer

Hirokazu Okudaira, M.D. (Allergology)

Yoshikata Misaki, M.D. (Rheumatology)

Fujio Takeuchi, M.D. (Rheumatology)

Zen-ichiro Honda, M.D. (Rheumatology)

Assistant

Tetsuji Sawada, M.D. (Rheumatology)

Ryoichi Tanaka, M.D. (Allergology)

Yoshinori Komagata, M.D. (Rheumatology)

Hiroko Kanda, M.D. (Rheumatology)

Masao Yamaguchi, M.D. (Allergology)

Takeshi Suzuki, M.D. (Rheumatology)

Kimito Kawahata, M.D. (Rheumatology)

Homepage <http://>

Introduction and Organization

The Department of Allergy and Rheumatology presently consists of 12 staff mentioned above, who preside over 4 medical staff, 12 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. Bed-

side 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 by means of autoantigen gene cloning and epitope mapping.
- 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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Commun. 341:94-100, 2006.

Department of Infectious Diseases (Internal Medicine)

Professor

Kazuhiko Koike, M.D., Ph.D.

Associate Professor

(To be appointed)

Associate

Yasuo Ota, M.D., Ph.D.

Homepage <http://infect.umin.jp/>

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, 9 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 dis-

eases 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, Yasuo Ota, Hiroshi Yotsuyanagi, Yoshizumi Shintani, Takeya Tsutsumi, Satoshi Itoyama, Takatoshi Kitazawa, Kuniko Ueda, Shuji Hatakeyama, Kunihiisa Tsukada, Shu Okugawa, Miki Kawada, Shintaro Yanagimoto, Yohko Nukui, Katsutoshi Abe, Atsuhito Fukushima, Keita Tatsuno, Sohei Harada, Koji Goto, Mahoko Kamimura.

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Patients with Chronic Hepatitis C. **World J Gastroenterol** 2006 in press.

Department of Stress Science and Psychosomatic Medicine

Professor

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

Associate Professor

Hiroaki Kumano, M.D., Ph.D.

Associate

Kazuhiro Yoshiuchi, M.D., Ph.D.,

Masami Nishikawa, M.D.

Homepage <http://psmut.umin.ac.jp/>

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, non-ulcer dyspepsia, hypertension, diabetes mellitus, or hyperthyroidism. We are responsible for 8 beds in the Tokyo University Hospital. Our teaching staff consists of one professor, one associate professor, two associates, and 5 adjunct professors, and other members are 2 senior residents, 9 graduate students, and 10 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 either an elder associate or an 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 2005 April to 2006 March, roughly 80 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 2005 April to 2005 March, the total number of about 600 patients newly visited our outpatient clinic.

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 (net 4 days), 'clinical clerkship' for 3 to 4 sixth grade students lasting 4 weeks each, and a clinical lecture on panic disorder for sixth grade students. We are trying hard 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 life-style-related diseases, cancers, and multiple chemical sensitivities, we are investigating their pathophysiology and psychopathology through assessing bio-psychobehavioral time-series data, various questionnaire data, higher brain function, and autonomic nervous function. We are also actively conducting basic as well as clinical research on eating-related substances or on stress and sexual hormones.

Some representative research topics are as follows:

- 1) Investigation on neurobehavioral basis of stress-related diseases such as tension-type headache, eating disorder, insomnia, panic disorder, and multiple chemical sensitivity by use of ecological momentary assessment (EMA) methods.
- 2) Interventional studies with cognitive behavioral treatment or relaxation procedures on tension-type headache, panic disorder, or insomnia.
- 3) Behavioral scientific studies of stress-related diseases such as irritable bowel syndrome, eating disorders, panic disorders, depression, cancer, and chronic renal failure by use of various questionnaires and physiological data.
- 4) Elucidation of brain processes closely related to mind/body correlation in stress-related diseases such as eating disorders and panic disorders or in meditative states in healthy people by use of brain functional analysis methods such as positron emission tomography, electroencephalography, and event-related potentials.
- 5) Investigation on neuroendocrine mechanisms related to the symptomatic improvement during treatments on eating disorders or on male climacteric syndrome.

Nine graduate students and 10 researchers are actively conducting their researches along with our teaching staff. We are also collaborating with many scientists belonging to other departments either in Japan or abroad. Research conferences are held once a month, where one of graduate students takes charge and presents his or her research activities for open discussion by all members of our department.

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Internal Medicine

3. Clinical Laboratory Medicine and Pathology

Department of Transfusion Medicine and Immunohematology

Professor

Koki Takahashi, M.D., Ph.D.

Associate

Nobukazu Hori, M.D., Ph.D.,

Nelson H. Tsuno, M.D., Ph.D.,

Aki Kamijo, M.D., Ph.D.

Homepage <http://172.27.30.16/yuketsu/s-index.html>

Introduction and Organization

The department of Transfusion Medicine was established in 1949, initially as an internal provisional measure, and officially in 1966. In 1997, when the Graduate School of Medicine was established at the University of Tokyo, the Department of Transfusion Medicine, a chair of the Internal Medicine Division, was created. In 1984, Professor Hiroshi Toyama assumed as the first Professor of the department. Professor Toyama had great achievements by publishing “Transfusion Medicine” (actually in its 3rd. edition), which is the bible of transfusion medicine in Japan. Other achievements from the department are as follows. Dr. Kazuo Okochi, ex-lecturer of the department, introduced the Australia antigen (actually known as HBsAg) testing of blood products, ex-Professor Takeo Juji clarified the mechanisms of graft-versus-host disease (GVHD), a serious post-transfusional complication, and the previous professor, Professor Yoichi Shibata has contributed enormously in the field of platelet serology.

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 function of the department is the control, preservation, and provision of blood products and their derivatives for transfusion. 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, tests for transfusion-transmitted infectious diseases are routinely performed, and in case of post-transfusion complication, the department takes measures to help diagnosis and treatment. The department also actively takes part in autologous blood collection and preservation, and in January 2006, the outpatient clinic for autologous blood transfusion, the first established in Japan, was started. In this outpatient clinic, 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 patient's status and needs. Preservation and provision of autologous blood are also function of the department. Additionally, immunotherapy of cancer patients and patients with recurrent abortion, and collection and preservation of peripheral blood stem cells are also important clinical activities of the department.

- 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 habitual abortion;
 - 3) Collection and preservation of peripheral blood stem cells for transplantation;
 - 4) Dendritic cell-based cancer immunotherapy.
 - 5) Anti-angiogenic therapy of cancer.

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 cell, leukocyte, and platelet antigens, the post-transfusional complications, transplantation immunology, immunotherapy, and stem cell biology are the main themes of the department. The HLA typing, which is an essential test for stem cell and organ transplantations, and platelet and granulocyte antigens, as well as plasma antigens, which are involved in post-transfusional complications, are investigated by serological and DNA-based methods. Transplantation immunology, including stem cell biology, and development of immunotherapeutic strategies to treat cancer patients and patients with recurrent abortion are also being performed. Recently, development of new materials for medical use is being researched. Following are the main themes.

1. Detection of platelet alloantigens and antibodies and their role in the transfusion practice.
2. Diagnosis and prevention of post-transfusional complications and thrombocytopenic purpura of the newborn.
3. Clinical application of refrigerated and frozen-stored blood for autologous transfusion in surgical patients.
4. Study on the mechanisms of transfusion-associated GVHD and its prevention.
5. Development of a new methodology for platelet cross-match.
6. Detection and characterization of anti-endothelial cell antibodies, and study on their role in the pathogenesis of inflammatory and autoimmune diseases, as well as in organ transplantation.
7. HLA and HPA genotyping.
8. Study on the effect of irradiation and filtration on platelet function.
9. Development of a new methodology for evaluation of platelet function.
10. Development of new strategies for the treatment of cancer patients, by targeting the tumor vasculature.
11. Study on the mechanism of antigen presentation by

dendritic cells.

12. Dendritic cell-based immunotherapy of cancer patients.
13. Ex-vivo expansion of hematopoietic stem cells and their clinical application.
14. Investigation of the self-renewal and differentiation of multipotent hematopoietic stem cells.

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Reproductive, Developmental and Aging Sciences

1. Obstetrics and Gynecology

Department of Reproductive Endocrinology

Professor

Yuji Taketani

Osamu Tsutsumi

Associate Professor

Tetsu Yano

Lecturer

Koji Kugu

Mikio Momoeda

Yutaka Osuga

Toru Takeuchi

Toshihiro Fujiwara

Homepage

Organization

The Department of Reproductive Endocrinology is organized by two professors, one associate professor and five 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 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 eighteen years. Conventional IVF-ET is mainly indicated to cases with tubal factor, mild male factor, immunological factor or of unexplained infertil-

ity factor. In case of severe male factor or other fertilization disorder intracytoplasmic sperm injection (ICSI) is performed. Now we have about 250 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 (130 cases), laparoscopic hysterectomy (16 cases), laparoscopically assisted vaginal hysterectomy (16 cases), laparoscopic or laparoscopically assisted myomectomy (50 cases), diagnostic laparoscopy for infertility (12 cases) laparoscopic surgery for ectopic pregnancy (10 cases), hysteroscopic surgery (55 cases) and so on, which make a total of 316 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

Associate Professor

Tetsu Yano

Lecturer

Toshiharu Yasugi

Homepage

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 Japa-

nese 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 antibodies (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 pres-

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

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

1 Human Scribble

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

downregulation of hScrib mRNA expression and ubiquitin-mediated degradation of hScrib by E6 and E6AP led to the complete decrease of hScrib expression during the process of carcinogenesis from H-SIL to invasive cancer. These data underscore the importance of hScrib in the construction of tissue architecture and prevention of cancer development.

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.

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 endo-

metrial, 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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Department of Perinatal Medicine

Associate Professor

Shiro Kozuma

Tomoyuki Fujii

Lecturer

Yoshimasa Kamei

Homepage

Organization

The Department of Perinatal Medicine is organized by two associate professors 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 the accurate diagnosis of intrauterine growth retardation possible. 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 120 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 is indicated. The inoculation is usually performed four to six times in every two or three weeks. In our clinic, after the immunotherapy, their pregnancy outcomes have extremely improved in these 10 years. Now the successful reproductive rate has achieved over 80%.

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Reproductive, Developmental and Aging Sciences

2. Pediatric Sciences

Department of Pediatrics, Department of Developmental Pediatrics

Professor

Takashi Igarashi, M.D., Ph.D.

Associate Professor

Masashi Mizuguchi, M.D., Ph.D.

Takashi Sekine, M.D., Ph.D.

Lecturer

Hiroshi Watanabe, M.D., Ph.D.

Hitoshi Kato, M.D., Ph.D.

Masaru Takamizawa, M.D., Ph.D.

Junko Takita, M.D., Ph.D. (Department of Cell Therapy and Transplantation Medicine)

Associate

Kazuhiko Shibuya, M.D., Ph.D.,

Hiroko Sugimura, M.D.,

Jun Inatomi, M.D., Ph.D.,

Hirotsugu Kano, M.D., Ph.D.,

Ken Satoh, M.D.,

Hiroki Yasudo, M.D., Ph.D.

(As of Dec. 1, 2005)

Komei Ida, M.D.,

Katsuyoshi Ko, M.D.,

Hiroshi Ono, M.D.,

Masakazu Mimaki, M.D., Ph.D.,

Shinya Tsuchida, M.D.,

Yoshitaka Yokoyama, M.D.,

Keiji Goishi, M.D.,

Fumie Kimura, M.D.,

Kan Takahashi, M.D.,

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

Introduction and Organization

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

Our staff consist of 1 professor, 2 associate professors, 5 lecturers, 15 associates, 6 residents, 1 clinical fellow, 1 research fellow, 12 graduate students and 1 foreign pediatrician as of Dec 1, 2005.

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 the

pediatric and pediatric surgery ward, there are 96 beds including 9 beds in the neonatal intensive care unit (NICU), 6 beds in the growth care unit (GCU) and 26 beds in the high care unit (HCU). In NICU we are taking care of small premature babies weighing 400g to 3,000g with or without various complications. 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, metabolic disorders, immunological/allergic disorders (common variable immunodeficiency, chronic granulomatous disease, bronchial asthma, etc.), renal and urinary tract diseases (nephrotic syndrome, chronic glomerulonephritis, purpura nephritis and renal and urinary tract anomalies), endocrinological disorders and psychosomatic diseases are admitted in the wards. So far 70 patients received hematopoietic stem cell transplantation. 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.

We have a clinical conference and a grand round in the Tuesday afternoon. Jeffrey C. Fahl, M.D., Professor of Pediatrics, Division of Pediatric Gastroenterology and Nutrition attended this conference and gave several lectures from January to April, 2006. He also opened special education course for junior doctors in very Friday evening during that time. In the Thursday evening, we have a special clinical conference. We also join in conferences several times a month with cardiac surgeons, obstetricians, pediatric surgeons and pediatric psychologists. In addition, each subspecialty group has its own meeting and clinical round.

Many patients with significant disorders stay long in the hospital. We provide an official in-hospital school "Kodama Gakkyu" where patients receive education and have chances to communicate with each other and their parents in the hospital. "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. It is a great pleasure for both the patients and their mothers. We also provide various activities 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 had two child care specialists in the pediatric ward in April, 2006.

(As of Dec 1, 2005)

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 as cardiology, hematology/oncology, neurology, endocrinology, immunology, nephrology, hepatology and international medical cooperation. 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 few years are listed as follows: molecular and epidemiological analysis of cancer disposition, molecular analysis of hereditary renal diseases, primary immunodeficiency, neuromuscular diseases and certain syndromes with and without congenial cardiac defects, hemodynamics of pulmonary circulation, and electrophysiological studies of epidemic disorders. The Kanto district registration center for children's cancer is located in our Department.

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Department of Pediatric Surgery

Professor

Kohei Hashizume, M.D., Ph.D.

Lecturer

Yutaka Kanamori, M.D., Ph.D.

Associate

Masahiko Sugiyama, M.D.,
Makoto Komura, M.D., Ph.D.

Tetsuya Tomonaga, M.D., Ph.D.,

Homepage <http://square.umin.ac.jp/pedsurg/index.html>

Introduction and Organization

The Department of Pediatric Surgery was founded in 1971 as a clinical department in the hospital, and then became a department in the faculty of medicine in 1989. Pediatric surgery is a rather new speciality in the field of surgery. It includes neonatal surgery, pediatric surgical oncology, pediatric emergency medicine, transplantation surgery in childhood, and even fetal surgery. Our department has the longest history as an independent department of pediatric surgery in all the national university hospitals. Although the number of staff is small, we keep very tight relationship with other departments of pediatric surgery in children's hospitals, and general hospitals and also research centers in Japan and abroad. So the clinical and research activity is very productive compared to the number of the staff. In February 1997 Hashizume became the professor of the department and a new organization has started.

Clinical activities

We have 12 beds in the ward as proper, but we can use 4 to 8 more beds if needed. There is a pediatric intensive care unit (PICU), in which

surgical neonates, postoperative cases after major operations, and those cases which needs respiratory support are cared. An average of 300 operations are performed a year, in which included are 20 to 30 neonatal cases, ten cases with malignant tumors, and several cases of tracheal resection or tracheoplasty which is a very new and challenging field in pediatric surgery. Also since April 1996 living-related liver transplantation (LRLT) program has implemented in our department in cooperation with the Department of Transplantation and Artificial Organs. We moved to the new wards 3 years ago, and because we use common wards with the department of pediatrics, our cooperation has become even tighter than before.

Teaching activities

For the M2, M3, and M4 students, general pediatric surgery and neonatal surgery are lectured by the professor and the lecturer. Bedside education program is also provided for the M3, and M4 students. 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 hepato-

biliary surgery, and pediatric emergency medicine which includes practice of cardiac massage and intra-tracheal intubation using dolls for the practice. Although the duration of bedside education of pediatric surgery is only for 5 days, it has a good reputation in students. Concerning postgraduate education, there are 5 postgraduate students, one of them are from abroad. They study very wide variety of topics, such as anti-oncogene of neuroblastoma in chromosome 1p, abnormalities of beta-catenin in hepatoblastoma patients, mechanism and prevention of reperfusion injury in liver transplantation and small intestinal transplantation, and a new immunological therapy of neuroblastoma using dendritic cells.

Research activities

In Department of Pediatric Surgery, we have 4 research groups, namely oncology group, hepatobiliary and transplantation group, prenatal developmental group, and gastro-intestinal group.

Professor Hashizume supervises the oncology group. Studies going on in this group are multi-drug resistance in pediatric solid tumors, suppressor oncogenes in solid tumors such as neuroblastoma, Wilms' tumor, and Ewing's sarcoma. Professor Hashizume also supervises the hepato-biliary and transplantation group. Main topics studied in this group are related to liver transplantation, small intestinal transplantation, new immunosuppressive drug, and pathology of biliary atresia. Lecturer Kanamori supervises the gastro-intestinal group. The main concern in this group is growth and migration of intestinal T-cells related to newly found intestinal lymph-apparatus, cryptosporidiosis. Also change of intestinal flora and bacterial translocation in short bowel syndrome patients are studied. Recently we introduced probiotics and synbiotics for the treatment of these patients and we found they started to grow very rapidly after the introduction of them. Professor Hashizume supervises the prenatal developmental group. The main topic in this group is congenital diaphragmatic hernia (CDH), which is one of the

most intractable congenital anomalies in the field of pediatric surgery. Pathophysiology of CDH and a possibility of fetal treatment of CDH with severe hypoplasia of lungs are intensively studied. Now we are doing a research with the department of obstetrics using fetal lambs. We are looking for the effects of tracheal occlusion using specially designed balloon and the result is very promising so far.

Publishing

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Department of Pediatric Oncology

Professor

Kohei Hashizume, M.D.,Ph.D.

Lecturer

Yutaka Kanamori, M.D.,Ph.D

Associate

Masahiko Sugiyama, M.D.,
Makoto Komura, M.D., Ph.D

Tetsuya Tomonaga,M.D., Ph.D.,

Homepage <http://square.umin.ac.jp/pedsurg/index.html>

Introduction and Organization

When the graduate school of medicine started in the University of Tokyo, the professor of pediatric surgery at that time became the professor of pediatric oncology concurrently. So the staff of the Department of Pediatric Oncology is common with the staff of the department of Pediatric Surgery. It consists of a professor, a lecturer, and 4 assistants. Actually, however, the oncology group in the Department of Pediatrics led by Dr. J. Takita is a part of the department, and their contribution to the department is tremendous.

Clinical activities

In clinical activities, oncology group in the department of Pediatric Surgery and the oncology group in the department of Pediatrics always keep contact and treat the patients with pediatric malignant diseases cooperatively. When a patient with malignant disease is admitted to the ward, the treatment principles are determined at the conference attended by the doctors from the both groups. Sometimes patients with pediatric malignancies in the region of neurosurgery, orthopedics, or ophthalmology, are also admitted to the pediatric ward, and they at first receive chemotherapy by pediatric oncologists and an extirpation of the tumor is conducted by surgeons later. This is so-called multi-disciplinary approach and it is well established in the pediatric on-

cology. This approach contributes greatly to the improvement of the prognosis of pediatric malignancies.

Education

Lectures of pediatric oncology are performed by pediatric oncologists and pediatric surgeons. At present there are 3 lectures by pediatric oncologists and 1 lecture by pediatric surgeons. Children with malignant diseases tend to be admitted long time, so in BSL (bed side learning) they have good chance of being charged by students. And it is also a good experience for students to be in charge of patients with malignant diseases. They learn not only the therapies and examinations of pediatric malignant diseases, but also the long-lasting fight against malignant diseases by patients and their family.

Research

The themes of research in the department are various. Just a few of them are presented here. They include 1) significance of WT-1 gene mutations in Wilms tumor, 2) abnormalities of beta-catenin in liver tumors in children, 3) tumor-suppressor genes in neuroblastoma supposed to be resided in the short arm of no. 1 chromosome, 4) new tumor suppressor gene in pediatric malignant solid tumors and leukemias, 5) examination of genes at the breakpoints in leukemias. In 1), we re-

cently have found a novel mutation of WT-1, and contributed to the understanding of the mechanism of tumorigenesis in Wilms tumor. In 2) we found for the first time, that not only in malignant tumors of the liver but also in liver adenoma there are some abnormalities of beta-catenin. About 3), we study very intensively using quite a various kinds of methods, but have not yet succeeded to determine the tumor suppressor gene in this region. This area is the area where most fierce competition is going between many laboratories in the world. In 4) we clarify the function of translocated gene in the development of Rubinstein-Taybi syndrome. In these most advanced areas of research, it is almost impossible to perform researches in a single laboratory, and we co-study and change information constantly with many laboratories in Japan and abroad.

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Reproductive, Developmental and Aging Sciences

3. Aging Sciences

Department of Geriatric Medicine

Department of Aging Research

Professor

Yasuyoshi Ouchi, M.D., Ph.D.

Associate Professor

Masahiro Akishita, Ph.D.

Lecturer

Satoshi Inoue, M.D., Ph.D.,

Shinji Teramoto, M.D., Ph.D.

Masato Eto, M.D., Ph.D.

Associate

Katsuya Iijima, M.D., Ph.D.,

Sumito Ogawa, Ph.D.

Tomohiko Urano, Ph.D.,

Yumiko Ohike, Ph.D.,

Hiroshi Yamamoto, M.D.

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

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 respirology, cardiology, neurology, hematology, endocrinology, and bone metabolism, besides the general geriatric internal medicine.

We are trying to elucidate the pathophysiology of aging process and understand elderly patients from viewpoints of basic aging science using molecular biology technique and clinical aspects using the recent advancement of technology and geriatric assessment.

Clinical activities

In the clinical ward, there are around 20 patients who are taken care of by junior, senior and chief residents of our staff. Because senior and chief residents are very experienced, they team up with a junior resident, give instructions as to the assessment of the patient's problem, making of future plans, and help the 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 300 new and a total of 16,000 patients visit the out-patient clinic in a year.

Teaching activities

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 interrogation and physical examination, interpretation of laboratory tests, and actual medical proce-

dures. 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 activities

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.

Shinji Teramoto, Yasuhiro Yamaguchi, Hiroshi Yamamoto, Yoko Hanaoka, Masaki Ishii, Mihoko Takizawa

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.

Yasuyoshi Ouchi, Masahiro Akishita, Masato Eto, Katsuya Iijima, Sumito Ogawa, Yumiko Ohike, Taro Kojima, Hidetaka Ota, Hiroko Hashimoto, Kazushi Nomura

Neurology unit

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

Yumi Kameyama, Kiyoshi Yamaguchi, Aya Takemura

Osteoporosis and endocrinology unit

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

Satoshi Inoue, Tomohiko Urano, Atsushi Shionoiri, Kotaro Azuma, Takahiko Usui, Hiroyuki Kinoshita, Ken'ichi Takayama

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Surgical Sciences

1. Surgery

Department of Thoracic Surgery

Professor

Takamoto, Shinichi

Associate Professor

Nakajima, Jun

Staffs

Murakawa, Tomohiro and Fukami, Takeshi

Homepage URL: <http://ctstokyo.umin.ne.jp/>

History

Clinical and basic researches of the thoracic surgery has 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 treatment of the tuberculosis in our country. After 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 ~).

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, post-graduates, 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 200 surgeries are performed annually in the department.

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 diseases

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 thoracoscopic 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.

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.

The following are the major themes under research:

(1) New oncogenes or suppressor oncogenes of the lung cancer

- (2) New methods for quantitative analysis of the DNA methylation of the lung cancer.
- (3) Clinical studies on the less-invasive surgical treatment of the thoracic malignancies
- (4) Analysis of the factors influencing the prognosis of lung cancer or mediastinal neoplasms
- (5) Adoptive anticancer immunity of the autologous gamma-delta-T-cell
- (6) Mechanisms of acute or chronic rejection of the allogeneic trachea graft.

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Department of Cardiothoracic Surgery

Professor

Shinichi Takamoto, M.D.

Associate Professor

Arata Murakami, M.D.

Lecturer

Noboru Motomura, M.D.,
Minoru Ono, M.D.

Teturo Morota, M.D.,

Associate

Tetsuhiro Takaoka, M.D.,
Tetsuo Doi, M.D.

Tetsufumi Yamamoto, M.D.,

Homepage <http://ctstokyo.umin.ne.jp/>

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 poste-

rior-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 Departments, 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 five Associates (two of them are in the US for research and clinical training).

Clinical Activities

Clinical conference starts at 7:15 am in weekdays. Regular surgery is scheduled on Monday, Wednesday and Friday. Patient round is on Tuesday 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 2005 is about 300, 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. The University Hospital was approved by the government as the fourth cardiac transplantation center in Japan in 2002.

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 four-year general surgical training. 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) treatment of end-stage heart failure by ventricular assist device, 5) a new technique of aortic valve sparing root replacement and its hemodynamic evaluation, 6) regeneration of ischemic myocardium by growth factor, 7) postoperative adhesion-proof membrane, 8) treatment of acute and chronic rejection after heart transplantation.

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Department of Gastrointestinal Surgery

Professor:

Michio Kaminishi, M.D.

Lecturer:

Sachiyo Nomura, M.D.

Associate:

Hirokazu Yamaguchi, M.D.

Kouji Nozaki, M.D.

Kazuhiko Yamada, MD.

Akemi Yoshikawa, M.D.

Ikuo Wada, M.D.

Nobuyuki Shimizu, M.D.

Tetsuya Ueda, M.D.

Atsushi Kaneda, MD.

Kazuhiko Mori, M.D.

Homepage

General Affairs:

Since 2001, the former Third Department of Surgery, which was located in a branch hospital of the University of Tokyo, has been divided into two departments, the Department of Gastrointestinal Surgery and the Department of Metabolic Care and Endocrine Surgery, in line with the integration of the main and branch hospitals the elevation to a department in the graduate school of medicine at our university. Our research activities in both departments have been well organized and ultimately successful by maintaining a close connection. The Department of Gastrointestinal Surgery presently comprises one Professor, one Lecturer, one Hospital Lecturer and nine associates.

With the prolongation of life expectancy, there are increasing numbers of multi-morbid patients requiring multi-organ treatment, as well as a greater need for multidisciplinary approaches to the patients. Our clinical and research activities have for the most part received the cooperation of members in the Department of Metabolic Care and Endocrine Surgery as well as those in other surgical departments at the University of

Tokyo.

Our fundamental principles of patient treatment are comprehensive patient care which includes pre-, peri-, and postoperative management of the diseases as well as patient care over long-term postoperative periods which often extend to the terminal stage. We believe that patient care encompassing the entire lifespan provides a wealth of valuable information concerning the appropriateness of current treatment strategy, the establishment of new surgical designs, the development of new basic research activities which can much contribute to clinical fields, and indications of desirable modes of terminal care.

Fostering good surgeons as well as scientists who meet both clinical and academic needs has always been the guiding principle of our Department.

Educational Activities:

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

rather than mere students during their bedside Learning. They learn generic patient care which encompasses not only perioperative management of diseases but also non-surgical management of postoperative disorders and terminal care. Our educational system provides medical students with a great deal of practical information from the medical point of view as well as better opportunities to ponder the implications of life and death.

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

Research Activities:

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

- 1) Carcinogenesis of gastrointestinal cancer
 - Diversity of gastrointestinal carcinogenesis
 - Gender differences in gastrointestinal cancers
 - Roles of sex hormones in gastrointestinal carcinogenesis
 - Monoclonality of intestinal metaplasia
 - Roles of *Helicobacter pylori* infection in gastric carcinogenesis
 - Interaction between cancer and interstitial tissue
 - Experimental evaluation of promotive mechanisms of gastroduodenal reflux and denervation of the gastric mucosa in gastric remnant carcinogenesis
 - Preventative roles of PPAR γ in gastric carcinogenesis
- 2) Molecular mechanisms of gastrointestinal tract cancer
 - 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 pre-operative case conferences on Tuesday, Wednesday and Thursday morning, respectively, and a journal club on Monday. We also have a specialized upper gastrointestinal case conference on Tuesday evening. Nursing-staffs have meetings with medical doctors on every Friday to ensure a high quality of patient care during the patients' hospital stay.

Generally, elective surgery is scheduled on Tuesday, Wednesday and Thursday. The statistics for 2005 show more than 250 cases of elective surgery and emergency surgery. All residents and medical personnel work many extra hours with high motivation whenever it is necessary for the good of the patients.

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Department of Hepatobiliary Pancreatic Surgery and Department of Artificial Organ and Transplantation Surgery

Professor

Masatoshi Makuuchi, MD

Associate Professor

Norihiro Kokudo, MD,

Yasuhiko Sugawara, MD

Lecturer

Yoshifumi Beck, MD,

Hiroshi Imamura, MD,

Keiji Sano, MD

Associates

Masami Minagawa, MD,

Katsutoshi Naruse, MD,

Hideki Abe, MD,

Wei Tang, MD,

Kiyoshi Hasegawa, MD,

Sumihito Tamura, MD,

Yasushi Midorikawa, MD,

Junichi Kaneko, MD,

Yasuji Seyama, MD

Homepage

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. A professor and chairman, two associate professors, three lecturers, and nine associates take part in inpatient and outpatient care as well as teaching and research activities. Department of plastic surgery, anesthesiology and staff of intensive care unit assist us in performing liver transplantation. Research on artificial liver is actively performed by Dr. Katsutoshi Naruse.

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.

From January 1996 to December 2005, the Pediatric Surgery Division and our department performed around 350 living donor and one deceased donor liver transplantation. The operative mortality is around 5%. Clinical conferences are held every day in which the laboratory data and clinical status of the transplants are discussed. Professor's ward round for inpatients is performed on Tuesday, Thursday and holidays. Out patient clinic is conducted in collaboration with other department of surgery. We have both general and special outpatient clinic. Specialist surgeons in liver transplanta-

tion surgery are in service on Monday, Tuesday and Thursday.

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.

Doctor course students are doing research work under the supervision of the professor and the staff members. If they think it necessary, they can participate in clinical patient care as a junior specialist surgeon.

Residents learn basic patient care and operative procedures at the university hospital. Subsequently they are sent to subsidiary hospitals for two years to learn further surgical activities. After this postgraduate training course they decide whether they take a doctor course.

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Department of Urology

Professor

Tadaichi Kitamura, M.D., Ph.D.

Associate Professor

Takumi Takeuchi, M.D., Ph.D.

Kyoichi Tomita, M.D., Ph.D.

Lecturer

Akira Ishikawa, M.D., Ph.D.

Haruki Kume, M.D., Ph.D.

Hiroaki Nishimatsu, M.D., Ph.D.

Hiroshi Fukuhara, M.D., Ph.D.

Associate

Shinya Matsumoto, M.D.,

Tetsuya Fujimura, M.D.,

Motofumi Suzuki, M.D., Ph.D.,

Aya Niimi, M.D.,

Chen Qin, M.D., Ph.D.,

Shizue Nyomura, M.D.,

Ken'ichi Tajima, M.D.,

Ryuji Tabata, M.D., Ph.D.,

Etsuko Tanaka, Akiko Hirose

Homepage [http:// www.h.u-tokyo.ac.jp/urology/](http://www.h.u-tokyo.ac.jp/urology/)

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 (especially, stress incontinence), 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, hyper-

thermic and laser therapies for BPH, and 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 42.0 per day from April 2004 to March 2005. More than half of inpatients suffer from urogenital cancers. Urolithiasis, benign prostatic hyperplasia, urinary incontinence and other many diseases are treated.

Elective operations are performed on Tuesday,

Wednesday, and Thursday. A total of 991 operations were performed in 2005. The main operations are total cystectomy 16 (ileal neobladder 7), radical prostatectomy 95, radical nephrectomy 32, transurethral resection of the bladder tumor (TUR-Bt) 109, transurethral resection of the prostate (TUR-P) 31, transurethral lithotripsy (TUL) 32, laparoscopic surgery 33.

A weekly clinical conference is held for discussing cases with difficult problems in detail and the best treatment is chosen for each case. Furthermore at the weekly professor's round on Wednesday, data of all in patients are presented and appropriate treatment strategies are recommended for them.

In out-patient clinic, services are provided from Monday to Friday. Patients assigned to specialized services as andrology, neurourology, urolithiasis, kidney and kidney transplantation receive sophisticated care on the particular day of the week.

The number of newly registered patients was 1290 and the total number of out-patients was 27,193 patient-days from April 2004 to March 2005.

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 groups with different clinical and research activities shown as follows. Our basic principles for research are in accord with the trends in modern medicine; improvement of quality of life, minimally invasive treatment, application of modern technology and/or basic science and cost-effectiveness. There are approximately 25 publications in English each year.

Nephrology group

Urolithiasis group

Kidney Transplantation group

Oncology group

Endourology group

Neurourology and Geriatric urology group

Andrology and Endocrinology group

Immunology group

Virology group

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Department of Surgical Oncology

Professor

Hirokazu Nagawa, M.D., Ph.D.

Lecturer

Joji Kitayama, M.D., Ph.D.

Clinical Lecturer

Shoichi Kaisaki, M.D.

Associate

Yoshiki Takei, M.D., Ph.D.,
Hironori Ishigami, M.D.,
Sinsuke Sito, M.D., Ph.D.,
Takamitsu Kanazawa, M.D.,

Giichiro Tsurita, M.D., Ph.D.,
Soichiro Ishihara, M.D., Ph.D.,
Sinsuke Kazama, M.D., Ph.D.,
Akio Hidemura, M.D., Ph.D.

Homepage <http://all-1su.umin.jp/>

Introduction and Organization

In 1997, 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 ma-

lignant 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 360 and 360 surgically treated inpatients in the 2004 and 2005 fiscal year, respectively. 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) Sentinel lymph node identification using nanobeads
- 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

Professor

Hirokazu Nagawa, M.D., Ph.D.

Associate Professor

Tetsuro Miyata, M.D., Ph.D.

Associate

Kunihiro Shigematsu, M.D., Ph.D.,
Hideo Kimura, M.D., Ph.D.,

Juno Deguchi, M.D., Ph.D.,
Seiji Nishikage, M.D.

Homepage <http://all-1su.umin.jp/>

Introduction and Organization

In 1997, 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 and four 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 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 242 and 279 surgically treated inpatients in the 2004 and 2005 fiscal year, respectively. 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 angiographic 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 in-

creasing 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. 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) Lower limb arterial circulation in a patient with end-stage renal disease assessed by near infrared spectroscopy
- 9) Microvascular permeability changes induced by PAF
- 10) Pharmacological analysis of microcirculation in in-vivo model
- 11) Mechanism of ischemic preconditioning of the 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

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Department of Metabolic Care and Endocrine Surgery

Professor;

Michio Kaminishi, M.D.,

Associate Professor;

Toshihisa Ogawa, M.D., Yoshikazu Mimura, M.D.,(Surgical Center)

Lecturer;

Hajime Kanauchi, M.D.,

Associate;

Makoto Kamamoto, M.D., Ei-ichi Tsuji, M.D.,

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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 additional 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 diseases without complications; 2) diagnosis and treatment of micro-breast lesions under ultrasonographic guides; 3) preoperative diagnosis for thyroid neoplasms and breast tumors based on telomere length and 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 endocrinologi-

cal 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 post-operative morbidity
- 5) Measurement of endotoxin activity through Toll-like receptor 4
- 6) Role of oxygen on local and systemic protein metabolism after major surgery
- 7) Ischemic preconditioning preserves renal dysfunction after ischemia-reperfusion
- 8) Telomere-length and telomere activity in the thyroid and the breast tumors
- 9) Application of Q-Fish in diagnosis of the thyroid and the breast tumors
- 10) Chemo-sensitivity in breast cancer

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Surgical Sciences

2. Sensory and Motor System Medicine

Surgical Sciences

3.Vital Care Medicine

Health Sciences and Nursing

1. Health Sciences

Health Sciences and Nursing

2. Nursing Sciences

International Health

1. International Social Medicine

International Health

2. International Biomedical Sciences

University Hospital

Clinical Divisions

University Hospital

Central Clinical Facilities

University Hospital

Pharmaceutical Service

**Center for Disease Biology and
Integrative Medicine**

Surgical Sciences

2. Sensory and Motor System Medicine

Department of Dermatology

Professor

Kunihiko Tamaki, M.D., Ph.D.

Associate Professor

Kanako Kikuchi, M.D., Ph.D.

Hironobu Ihn, M.D., Ph.D.

Lecturer

Mayumi Komine, M.D., Ph.D.

Takafumi Kadono, M.D., Ph.D.

Hidehisa Saeki, M.D., Ph.D.

Takahiro Watanabe, M.D., Ph.D.

Norihito Yazawa, M.D., Ph.D.

Associate

Makoto Sugaya, M.D. Ph.D.

Takashi Kakinuma, M.D. Ph.D.

Yayoi Tada, M.D., Ph.D.

Toshihiko Hoashi, M.D., Ph.D.

Masatoshi Jinnin, M.D., Ph.D.

Yuichiro Tsunemi, M.D., Ph.D.

Shinji Kagami, M.D. Ph.D. .

Shoichiro Yano, M.D., Ph.D.

Yuki Ohno, M.D.

Home page <http://www.h.u-tokyo.ac.jp/der/>

Introduction and Organizaition

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, two associate professors, four lecturers and nine 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, six 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

Professor

Isao Koshima, M.D.
Associate Professor

Hiroataka Asato, M.D.

Lecturer

Kotaro Yoshimura, M.D.

Associate

Koichi Gonda, M.D.,
Masayuki Okochi, M.D.,

Mutsumi Okazaki, M.D.,
Katsujiro Sato, M.D.

Homepage

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 90 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 2,700 new patients and the total number of revisiting patients are about 25,000 in a year. In the operating theater over 300 operations are achieved under general anesthesia, while in the outpatient clinic about 300 operations are achieved under local anesthesia in a year. Each week, the professor goes the round of inpatients on Wednesday morning. Preoperative and postoperative conferences and seminar that all members of the department should attend are held on Wednesday evening. Research conferences are held on every Thursday 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 bed side practice the students have the opportunity of seeing various diseases and disorders in the field of plastic surgery and attending outpatient clinics, surgical

operations and clinical lectures by faculty members. For graduate school students, microsurgical training program is undertaken in the laboratory room. In the postgraduate course, after completing the 6-year training program, a trainee can sit for the board examination of the Japan Society of Plastic and Reconstructive Surgery.

Research Activities

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

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

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Department of Oral-Maxillofacial Surgery

Professor

Tsuyoshi Takato, M.D., Ph.D.

Associate Professor

Takafumi Susami, D.D.S., Ph.D.

Yoshiyuki Yonehara, M.D., Ph.D.

Lecturer

Yoshiyuki Mori, D.D.S., Ph.D.

Ken Tomizuka, D.D.S., Ph.D.

Hisako Hikiji, D.D.S., Ph.D.,

Meiko Ohki, D.D.S., Ph.D.

Associate

Jun-ichi Kuroe, D.D.S.

Nobuhiko Kumazawa, D.D.S.

Katsumi Ohhashi, D.D.S.

Masako Matsuzaki, D.D.S., Ph.D.

Hideto Saijo, D.D.S., Ph.D.

Mamiko Wada, M.S.

Yukiko Suzuki, D.D.S.

Gen-ichiro Takagi, D.D.S.

Daichi Chikazu, D.D.S., Ph.D.

Yuji Ogihara, D.D.S., Ph.D.

Toru Ogasawara, D.D.S., Ph.D.

Homepage <http://plaza.umin.ac.jp/%7Eoralsurg/>

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 a wide variety of specialists, including oral surgeons, orthodontists and prosthodontists. We handle all diseases in the oral-maxillofacial region, such as congenital anomalies, jaw deformities, benign and malignant tumors, bone fractures and inflammation. Dental care for the patients who have systemic disorders and are 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 capacity of tissues, especially bone, periosteum, cartilage, perichondrium, vessels, nerve, skin, etc. At present, we are focusing on tissue engineering in research works especially in bone, cartilage, vessels. Professor Takato has established Tissue Engineering Division in Tokyo University Hospital and our department has two endowment departments: Department of Cartilage and Bone Regeneration (FUJI SOFT Inc.) and Department of Clinical Vascular Regeneration (Daiichi Pharmaceutical Co., Ltd.) in Tissue Engineering Division. These departments have 1 associate professor, 1 associate, and some graduate students in each. 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, and treat about 90 patients per day. Dental treatments for systemic diseases are mainly performed in this clinic. Dental surgeries such as extraction of impacted teeth, amputation of infected dental root and gingivoplasty are performed in the operation room. Dental implants are also set in an outpatient basis and often utilized in maxillofacial prosthodontic treatments in reconstructed jaws after surgical resection of malignant tumors. Facial growth control and tooth movements in patients with congenital facial anomalies such as cleft lip and palate are the most popular orthodontic treatment. Pre- and post-surgical orthodontic treatments combined with surgical correction of dentofacial deformities are another important role. Speech therapy to the patients with cleft lip and palate are being done by speech-language-hearing therapists in the same outpatient clinic.

In the ward, we have about 350 new inpatients and 330 cases are operated per year. The main surgical operations are primary closure of cleft lip and palate, secondary bone grafting in alveolar cleft, surgical correction of dentofacial deformities using maxillo-mandibular osteotomies, resection of malignant tumors followed by micro-surgical reconstruction by plastic surgeons, and correction of facial bone fractures. Both for in- and out-patients, we treat by multidisciplinary team approach consisted of oral and maxillofacial surgeons, orthodontists and prosthodontists. Recently, we carry out facial bone lengthening by distraction osteogenesis, and grafting the original artificial bone which is made by the 3D data of CT and tissue engineering technique for patients with dento-facial deformity.

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 reconstruc-

tion 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.

As for postgraduate dental students, we have a two years training course. This course aims to train for a wide range of dental treatments and to learn about medical cares. Various specialists instructed dental treatments for them in outpatient clinic. Carious treatments, periodontal cares and applications of dentures are taught 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.

Research

Research projects are made both clinically and basically on themes closely related to clinical problems. 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, fractures and temporomandibular diseases
- 3) Multidisciplinary treatment of malignant tumors in head and neck region
- 4) Combined surgical-chemical-radiological treatment for malignant tumors
- 5) Development of dental implant
- 6) Effects of arthrocentesis or therapeutic exercises for temporomandibular disorders
- 7) Non-surgical treatment system for facial bone fractures
- 8) Bone repair in dentomaxillofacial region using tissue engineering technique

Basic and experimental research:

- 1) Osteogenic capacity of periosteum
- 2) Capacity of perichondrial regeneration
- 3) Osteogenic capacity of growth plate
- 4) Development of various types of new skin flaps
- 5) Metabolism of poly ADP-ribose in DNA repair and

cell differentiation

- 6) Gene analysis of congenital anomalies of oral and maxillofacial region
- 7) Effect of free radicals on bone metabolism
- 8) Intracellular calcium handling on osteoblasts
- 9) Differentiation mechanism of osteoblasts in terms of cell cycle molecule
- 10) Osteochondrogenic differentiation of bone marrow derived mesenchymal stem cells by spheroid culture
- 11) Mandibular lengthening by floating bone method
- 12) Periodontal tissue regeneration on dental implants
- 13) Characterization of skin derived multipotent stem cells, especially differentiation mechanism into neuronal cell
- 14) Bone and cartilage repair in dentomaxillofacial region using tissue engineering technique

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Department of Orthopaedic Surgery

Professor

Kozo Nakamura, M.D., Ph.D.

Associate Professors

Yoshio Takatori, M.D., Ph.D.,

Hiroshi Kawaguchi, M.D., Ph.D.

Lecturers

Isao Ohnishi, M.D., Ph.D.,

Atsushi Seichi, M.D., Ph.D.,

Sakae Tanaka, M.D., Ph.D.,

Katsushi Takeshita, M.D., Ph.D.

Associates

Motoi Yamamoto, M.D., Ph.D.,

Tatsuro Karita, M.D., Ph.D.,

Hiroataka Kawano, M.D., Ph.D.

Ko Matsudaira, M.D., Ph.D.,

Toshiki Miura, M.D., Ph.D.

Hideya Itoh, M.D.,

Yuho Kadono, M.D., Ph.D.

Hiroataka Chikuda, M.D., Ph.D.,

Toru Akiyama, M.D., Ph.D.,

Toru Ogata, M.D., Ph.D.,

Nobuhiro Hara, M.D.,

Koji Osuka, M.D.,

Atsushi Fukai M.D.

Homepage <http://www.h.u-tokyo.ac.jp/ortho/>

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. Hence, we celebrate the centennial of the department this year.

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 motor 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, 12 medical staff members, and 11 part-time teachers.

Teaching activities

In undergraduate education, our department takes part in systemic lectures, diagnostic lectures, and problem based learning (PBL) for 4th year medical students, bedside learning and Clinical Clerkship for 5th year medical students, and clinical lectures for 6th year medical students.

Systemic lectures offer comprehensive presentation for covering basic knowledge of the concept, pathogenesis, pathology, diagnosis and treatment of various motor system disorders is performed. The 12 consecutive lectures cover bone and soft tissue tumors, spinal diseases, joint diseases (hand, shoulder, elbow, hip, knee, and ankle), sports injuries, traumatology, and rheumatoid diseases. In the diagnostic lectures, we teach diagnostic maneuvers and radiological diagnosis of a variety of skeletal diseases. PBL is offered to a small group work to learn medical humanity and systematic methods to develop medical research.

During the 10-day period of bed-side learning, students have opportunities to experience daily clinical care with residents as well as practicing with faculty members. We have developed an original text for the students to learn orthopedics effectively. They participate in clinical conferences and surgery, and make reports on diagnostic and therapeutic procedures. 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.

In clinical lectures, we present the clinical aspects of important skeletal diseases, and discuss with the students several points for reaching a diagnosis and planning a treatment. Compression myelopathy and osteoarthritis were focused on in 2004 and 2005, respectively.

For postgraduate education, junior residents join our department for 5-8 months. Since the training period is short, the residents are expected to experience emergency cases as often as possible. A postgraduate seminar and a basic research conference are held weekly. Twelve basic orthopaedic seminars by invited guest speakers were held in 2004 and 2005.

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, bone lengthening, knee, hand, elbow, shoulder, sports, peripheral nerves, and bone systemic disorders. A total of 42,504 patients visited the outpatient clinic from April 2004 through March 2005.

The ward has approximately 60 to 75 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, Tuesday and Thursday evenings.

Six hundred and eleven and 533 operations were performed in 2004 and 2005, respectively. These included cervical and thoracic spine (84 and 60), lumbar spine (19 and 8), scoliosis (8 and 8), rheumatoid arthritis (61 and 51), hip (99 and 95), knee (19 and 47), shoulder (8 and 2), hand (35 and 26), limb lengthening and reconstruction using external fixators (8 and 7), and tumor (59 and 61).

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.

Operations performed by the rheumatoid arthritis clinic group were primarily total joint arthroplasty, and they reported the usefulness of absorbable screws for wrist arthroplasty.

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 are now developing a long-life artificial joint using the MPC polymer in collaboration with the Department of Materials Engineering in Tokyo University.

The knee clinic group developed a new endoscopic anterior cruciate ligament reconstruction technique using the navigation system based on fluoroscopic images to realize ideal graft placement.

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

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 motor 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 elementary measurement
- 7) In vivo bone formation by cytokines and its clinical application
- 8) Molecular mechanism of age-related bone and cartilage disorders

In addition to the activities inside the department, we have established two endowment departments in the 22th Century Medical Center that deal with clinical research, which houses the largest clinical database of osteoarthritis patients in the world for the pursue of genomic and etiological research. Another endowment department is in the Division of Tissue Engineering, which seeks to aims develop epochal bone and cartilage regenerative medicine. Furthermore, we collaborate with the Center for Disease Biology and Integrative Medicine (CDBIM), and are developing nonviral gene delivery vectors (polyion complex micelles) and long-life artificial joints for clinical application in the near future.

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Department of Ophthalmology

Professor

Makoto Araie, M.D., Ph.D.

Associate Professor

Goji Tomita, M.D., Ph.D.,

Yasuhiko Tamaki, M.D., Ph.D.

Lecturer

Satoru Kato, M.D., Ph.D.,

Atsushi Tomidokoro, M.D., Ph.D.,

Makoto Aihara, M.D., Ph.D.,

Miyuki Nagahara, M.D., Ph.D.

Associate

Toshikatsu Kaburaki, M.D., Ph.D.,

Tomohiko Usui, M.D., Ph.D.,

Yasuo Noda, M.D., Ph.D.,

Koichi Mishima, M.D., Ph.D.,

Takashi Shigeeda, M.D.,

Akira Hirose, M.D.,

Ryuichi Ideta, M.D.,

Yasuo Yanagi, M.D., Ph.D.,

Yuji Inoue, M.D., Ph.D.,

Keiko Hayashi, M.D.,

Tae Arakawa, M.D.,

Kenji Sugisaki, M.D.,

Homepage <http://plaza.umin.ac.jp/ophl>

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 5000 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 2000 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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Department of Otorhinolaryngology and Head & Neck Surgery

Professor

Kimitaka Kaga, M.D., Ph.D.

Associate Professor

Tatsuya Yamasoba, Ph.D.

Lecturer

Kenichiro Ishio, M.D., Ph.D.,
Takahiro Asakage, M.D., Ph.D.,

Ken Ito, M.D., Ph.D.,
Kazunari Nakao, M.D., Ph.D.

Associate

Shinichi Iwasaki, M.D., Ph.D.,
Shotaro Karino, M.D.,
Yasuhiro Ebihara, M.D.,
Yoshinori Fujishiro, M.D.,
Miwako Kimura, M.D.,
Muneo Nakaya, M.D.

Kenji Kondo, M.D., Ph.D.,
Takaharu Nito, M.D.,
Chikako Yamada, M.D.,
Hiroko Watanabe, M.D.,
Kenta Watanabe, M.D.

Homepage <http://www.h.u-tokyo.ac.jp/orl/>

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. It has passed 105 years. Our department covers all otorhinolaryngological diseases and associated systemic diseases, and has specialized clinics in middle ear and inner ear diseases, hearing impaired infant and children, adult and elderly patients, facial palsy, vertigo and balance disorders, olfactory disorders and paranasal diseases, voice and speech disorders, taste and swallowing respiratory disorders, aphasia, central auditory disorders and head & neck cancers.

A professor, two associate professors, four lecturers and 15 associates participate in surgery, out-patient and

in-patient care as well as research and educational activities. Two associates are abroad at present for basic research in the U.S.A. and Australia. Moreover five Japanese graduate students, two Chinese foreign graduate students and one Bulgarian doctor 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 and a weekly temporal bone histology conference is held every Monday evening.

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 400 new patients visit monthly.

In the new inpatient hospital, 45 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. Peroperative and postoperative problems are checked and discussed by each group, the professor's and associate professor's rounds. Approximately 650 operations are performed annually.

Cochlear implant surgery over 100 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 third 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. Medical interviewing for cancer patients is prac-

ticed. During half and a week period, the students participate in surgery special clinics and practice of clinic examination such as otoscope, fiberscope auditory brainstem, caloric test and so on.

Research activities

Clinical and basic research activities are highly encouraged. Clinical research, which is supervised by senior doctors, is very actively pursued even by young residents. Case reports presentation and writing skills are regarded as important experience in order to develop young doctors' research activity and investigate important findings in patients. The clinical research is related to ear surgery, neurotology, audiology, head & 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.
- 2) Clinical application of otoacoustic emissions and auditory brainstem responses.
- 3) Histochemistry of olfactory epithelium in development and aging.
- 4) Clinical neurophysiology of the facial nerves focusing on degeneration and regeneration in patients.
- 5) Histochemistry of head and neck cancer pathology.
- 6) The central auditory cortex research using MEG.
- 7) Auditory brainstem response and speech and hearing after the newborn hearing screening.
- 8) Pathology and electrophysiology of the larynx.
- 9) Basic and clinical research on auditory brainstem implant.
- 10) Vestibular research on the oculomotor and balance systems in the brain.
- 11) Vestibular myogenic evoked potentials in cochlear implant and inner ear anomaly.
- 12) Hair cell physiology in the vestibular end organ.
- 13) Newborn hearing screening and language development in deaf children.
- 14) Myelination of central auditory and vestibular

pathway using MRI.

- 15) Physiology bone conduction innovation of bone conduction hearing and bilateral hearing.
- 16) Acoustic research on development of babbling in neonates.
- 17) 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

Professor

Fumio ETO, M.D., Ph.D.

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

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 the University of Tokyo Graduate School of Medicine. It belongs to the Sensory and Motor System Medicine Course of the Surgical Sciences Study Major. 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 rapid expansion of needs, acknowledgment of rehabilitation medicine was delayed in the frame of 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, and seven graduate school students are on the register in 2005.

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 central rehabilitation service department of 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 200 patients or more corresponding about 20% of the whole number of inpatients. We also see 10-12 people/day at the ambulatory rehabilitation setting. The numerical ratio of ambulatory patient is reduced to around half in comparison with that of 10 years ago in order to give priority to the clinical service corresponding to needs expansion of service to an inpatient.

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, neuromuscular diseases, bone and joint diseases, and cerebral palsy as well as on multidisciplinary team approach. 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.

Nine graduate school students entered by 2005 and two of them acquired a degree of Ph.D. and graduated. One of the graduate school students is a foreign student from Mongolia. She is a rehabilitation specialist physician in Mongolia, and is supported for her staying by the MEXT scholarship of Japanese government. Another graduate school foreign student is a Chinese doctor, who visited Japan by the own expense. In addition, a rehabilitation specialist doctor from Italy was registered as a study student for two years since 2003 to 2005, as the MEXT scholarship student of Japanese government. Other two specialist doctors from China by a scholarship of the Japan-China Medical Association or by the Chinese government scholarship stayed and were registered as a study student from 2004 to 2005.

Research activities

Our mission is to provide exceptional rehabilitation for our patients through clinical excellence and compassionate care, all dedicated to helping patients achieve their maximum functional capacity and highest quality of life. Another significant focal point of the department is research. The research objectives of the department are to make clear configuration of disabilities and to develop measures to reduce the obstacles for patients' independent living as well as to promote reintegration in their society. However, rehabilitation medi-

cine has not been recognized as an established course in the University of Tokyo, and there is no space of an exclusive research laboratory and medical office.

Two or more equipment (force platform, video operation analysis system, surface electromyography, and ataxiometer, etc.) are combined for the evaluation of walking and motion disturbances. Synchronous measurements such as the torque machines for the muscular power measurement and the surface electromyography are available. Using these has carried out the research, which clarifies the effect of shoe insole in healthy population and subjects with various gait disorders.

We also engage in research on development of appropriate training method for recovery from physical deconditioning state, or disuse syndromes. Usual activity performances may need the functional integration of respiratory, cardiovascular, and metabolic system, which adequately supplies energy to the locomotion system including not only musculoskeletal organs but also central and peripheral nervous system organs.

The development of evaluation method of the intellectual impairment and the physical fitness measurement are also important subjects of our research for an appropriate rehabilitation program. Unilateral neglect, or hemispatial neglect, is one of the serious obstruction factors of stroke rehabilitation.

The detailed pathophysiology of unilateral neglect is unknown. There may be several subgroups of clinical feature, and we engage in development of those differential assessment methods in unilateral neglect. In addition, we have used the event related potential and magnetoencephalogram (MEG) in order to reveal the liability lesion of unilateral neglect.

Acupuncture is now popular as a complimentary and alternative medicine in Europe and America. However, mechanism of the effect is still vague. We have examined the effects of acupuncture by using the measurement system of autonomic nervous function.

Under current poor condition of our research environment, however, the research projects may be recommended to be accomplished in cooperation with the laboratory and the organization outside the hospital. In collaboration with some outside laboratories we have studied a pathological mechanism of muscle atrophy, joint contracture and bone atrophy, which are main components of disuse syndromes.

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Surgical Sciences

3.Vital Care Medicine

Department of Anesthesiology

Professor

Kazuo Hanaoka, M.D., Ph.D.

Associate Professor

Hideko Arita, M.D., Ph.D.,

Tomoki Nishiyama, M.D., Ph.D.

Lecturer

Choku Yajima, M.D., Ph.D.,

Ryo Orii, M.D., Ph.D.

Associate

Hiroshi Sekiyama, M.D.,
Yuichiro Saito, M.D.,
Masahiro Suzuki, M.D.,
Makoto Ogawa, M.D.,
Masahiko Bogaki, M.D.,
Satoshi Kasahara, M.D.,
Ju Mizuno, M.D., Ph.D.

Makoto Ogawa, M.D., Nobuko Ito, M.D., Ph.D.,
Nobuhide Kin, M.D., Takayuki Kitamura, M.D.,
Toshiya Tomioka, M.D., Ph.D.,
Erika Sano, M.D., Masako Seyama, M.D.,
Yoshie Suzuki, M.D., Nagara Ono, M.D.,
Kaori Fujita, M.D., Kyung-Ho Chang, M.D., Ph.D.,

Homepage http://www.h.u-tokyo.ac.jp/patient/depts/aprc_md.html/
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Introduction and Organization

The Department of Anesthesiology was established in 1952. Our department has residents, chief residents and three researchers from China besides the members above. We introduce the activities about Teaching, Research and Clinical work of our department.

Clinical activities

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. From April 2004 to March 2006, we had 803 new patients and total number was 27000.

There are three beds in the ward and about 100 patients admitted. From the other department, about 1500 patients visited our clinic to control pain, and 1500 patients visited to have a preoperative consultation.

Anesthesia service including pre and post-operative care is given every day for elective and emergency surgery. Recently, the number of high risk or geriatric patients are increasing. In addition, more than 20% of the surgery (about 8000 cases in total per year) spends more than eight hours.

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 physiol-

ogy and the management of pain.

Research activities

There are six laboratories in our department and making clinical and basic research about respiration, circulation, neuro-physiology, shock, etc.

These themes of the research groups of our department are listed below.

- (1) Physiology of pain and the mechanisms of analgesia using spinal rat
- (2) Relationship between noxious stimuli and catecholamines in the anesthetized rat
- (3) Response to immunologic system against the endotoxin in the blood
- (4) Measurement of pulmonary vascular resistance of normal and pulmonary edema using rabbit
- (5) Mechanisms and the pharmacological analysis of non-depolarizing muscle relaxants in human
- (6) The effect of anesthetics upon pulmonary function
- (7) Mechanisms of H-typed epidural-spinal anesthesia
- (8) Inhalational anesthetics and rate potential
- (9) The effects of midazolam upon the spinal analgesic mechanisms
- (10) Analgesic mechanisms of hyperventilation
- (11) The interaction of central analgesic and spinal analgesic mechanisms
- (12) Development of skin surface anesthetics by lidocaine tape
- (13) Clinical assessment of the induction by midazolam combined with barbiturates
- (14) The effects of epidural buprenorphine and morphine on post-operative pain control
- (15) Clinical usefulness of patient-controlled analgesia (PCA)
- (16) Clinical assessment of stellate ganglion block
- (17) Assessment of anesthetic machines
- (18) The effects of peripheral sensory nervous activities by acupuncture
- (19) Clinical assessment of malignant hyperthermia
- (20) Basic research of the changes in transmission and distribution of gas with pulmonary lesion
- (21) Simulation of general anesthesia
- (22) Clinical assessment of anti-hypertensive agents
- (23) Basic and clinical assessment of benzodiazepine antagonist

- (24) Basic and clinical assessment of non-depolarizing muscle relaxants
- (25) Basic and clinical assessment of enkephalinase inhibitor
- (26) Prostaglandins and tissue blood flow of the liver and kidney
- (27) Relationship between sympathetic nervous system and cardiac function
- (28) Clinical assessment of pulse-oximeter
- (29) The effects of poly-enzyme inhibitor upon tissue microcirculation
- (30) Analgesic mechanisms of nociceptin in spinal rat
- (31) Assessment of Bispectral Index monitor
- (32) Clinical evaluation of drug challenge test
- (33) Analgesic mechanisms of laser treatment
- (34) Analgesic mechanisms of oriental herbal medicine
- (35) Clinical assessment of acupuncture
- (36) Development of device for Intubation
- (37) Analgesic efficacy of $\alpha 2$ agonist in a postoperative pain model

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Department of Emergency and Critical Care Medicine

Professor

Naoki Yahagi, M.D.

Lecturer

Yukio Tanaka, M.D., Ph.D.

Susumu Nakajima, M.D., Ph.D.

Associate

Shoichi Katada, M.D.,

Yoichi Kitsuta, M.D.,

Daisuke Yamaguchi, M.D.,

Takeshi Ishii, M.D.,

Tetsuya Inoue, M.D.,

Toshihiro Morita, M.D.,

Kyoko Komatsu, M.D.,

Tsuneo Suzuki, M.D.,

Yasushi Imai, M.D.

Staff

Shinji Matsuse, M.D.,

Makoto Furukawa, M.D.,

Hiroshi Shinbori, M.D.

Homepage: [//www.h.u-tokyo.ac.jp](http://www.h.u-tokyo.ac.jp)

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 16,800 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 optho-ENT evaluations. 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 ICU/CCU, MHCU and HCU.

The new Critical Care Center contains adult intensive care unit (ICU) of 8 beds, coronary care unit (CCU) of 6 beds, surgical high care unit (SHCU) of 36 beds, medical high care unit (MHCU) of 15 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 6,452 ambulance patients out of total 17,370 ER outpatients.

The new ER, four times the size of the present ER is scheduled to be built in 2006. The facility will have 5 consultation rooms, 4 specialized consultation rooms for dentistry, ophthalmology, otorhinolaryngology and gynecology, 2 resuscitation bays, 1 operating room and 11 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 patients in the 2004. In 2006, the number of beds in ICU will increase to 16 and the facility will include the 24 beds for the surgical ICU patients by 2007.

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, HCU and ICU/CCU in accordance with their critical condition. The surgical HCU 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 man-

agement, 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 are planning to set oxygen and medical suction equipment on the passageways in the new ER within 2006 fiscal year in order to treat the large number of disaster patients.

Teaching activities

1) Six hours of lecture for the 2nd year medical student, the topics include the prehospital emergency care, the initial evaluation of emergency patients, disaster medicine, serious infections disease, and medical equipment. Four hours of simulation training of Basic Life Support.

2) One month of clinical clerkship and 1 week of bed-side training for the 3rd year. ACLS Basic course (ICLS) is held for the participants in the clinical clerkship program, and successful completion of this course will enable students to be ICLS certified.

3) Clinical integrated lecture for the 4th year students includes diagnosis and treatment of serious patients using case studies of shock, conscious disorder, trauma, intoxication, infections disease, burns, hypothermia, and convulsion. After learning a ACLS course, students experience the real practice of emergency medicine as fellow passengers in the ambulance and as 2.5-day trainees in affiliated hospitals' emergency centers.

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

Junior residents are also assigned to ICU services to gain the knowledge of intensive care from pathophysiological and internal medicine's point of view.

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

As medical aspects of disaster management, we provide the residents with lectures based on MIMMS (Major Incident Medical Management and Support) program, triage training, and risk communication techniques using wireless network.

In addition, we produce the seminar for nurses such as medical support in the big earthquake.

Research activities

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

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Health Sciences and Nursing

1. Health Sciences

Department of Health Sociology

Associate Professor

Yoshihiko Yamazaki, Ph.D.(Dr.Hlth.Sc.)

Homepage <http://www.hlthsoc.m.u-tokyo.ac.jp/indexj.htm/>

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. The department consists of one Associate Professor (Head of Health Sociology), 33 graduate students (20 master course students and 13 doctor course students) including 2 international students and 18 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 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 Multi-

variate 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. In the fiscal 2004-05, the membership in each seminar above-mentioned was 25 – 30 and over.

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 2004-05, 13 MC students submitted Master Thesis and gained Master's Degree. Four DC students submitted Doctoral Dissertation and got Doctor's Degree. Eight graduate students have got a job as a university teacher, professor, or researcher.

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 these two years.

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

Norito Kawakami, M.D., D.M.Sc.

Assosicate Professor

Iwao Oshima, Ph.D.

Assistant Professor

Toshio Mori, Ph.D.

Homepage <http://plaza.umin.ac.jp/heart/>

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 is also obliged to educate graduate students in master and doctor programs in mental health. To accomplish this objective, the department has specialized lecture courses on mental health, which are held for 1.5 hours every Wednesday morning for 10 weeks in each semester; seminars; and field works on mental health for graduate students. These activities are conducted and supervised by the professor and assistant professor. We also have the department seminar every Wednesday evening, where relevant English articles are introduced by graduate students and a prominent guest speaker gives a lecture every other month.

Research activities

Due to broad interests of the staff members, the department has many research projects across diverse fields as follows: psychiatric epidemiology, social psy-

chiatry, mental health services research, community mental health, occupational mental health; psychiatric rehabilitation, clinical psychology, psychotherapy, child and adolescent psychiatry; and developmental disorders. The department staff members employ many research methodologies adopted from various fields, such as medicine, psychiatry, psychology, sociology, social work, nursing and education. We are conducting studies in collaboration with researchers in institutions and universities in and outside Japan.

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Department of Biostatistics / Epidemiology and Preventive Health Sciences

Professor

Yasuo Ohashi, Ph.D.

Associate Professor

Yutaka Matsuyama, Ph.D.

Lecturer**Associate**

Takuhiro Yamaguchi, Ph.D.

Yoichi Ito

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

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 in-

cluding 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 is providing lectures in a series of educational courses organized by ‘The Clinical Bioinformatics Research Unit’ established in 2002.

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. 'The Clinical Bioinformatics Research Unit' courses
 - 1) Introduction of Biostatistics required for biomedical research
 - 2) Methodology of Clinical Trials (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 Longitudinal Arteriosclerosis Study
 - Japan Diabetes Collaborative Study
- 5) Consultation Works

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Department of Social Gerontology

Professor

Ichiro Kai, M.D., M.P.H.

Associate

Miyako Takahashi, M.D., Dr.Hlth.Sc.

Tami Saito, M.Hlth.Sc.

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

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, five visiting lecturers, two associates and 17 graduate students (including six international students from Korea, China, Philippines and Nepal).

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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Department of Biomedical Ethics & Department of Health Promotion Sciences

Professor

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

Lecturer

Jung Su Lee, Ph.D.

Associate

Satoshi Kodama, Ph.D., Kenji Matsui, M.D., Ph.D.

Homepage [http:// www.ethps.m.u-tokyo.ac.jp/](http://www.ethps.m.u-tokyo.ac.jp/)

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. Ya-

suki 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. 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.

Staff members of the two departments include a professor, a lecturer, two associates, and a technical assistant. All five members, a total of eight lecturers from other organizations and nine visiting researchers contribute to department teaching and research activities.

Department graduate students included three master program students and five doctoral program students (including two international students from the USA and China) in 2004, and two master program students and five doctoral program students (including one international student from the USA) in 2005.

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. Two bachelor theses, three master theses, and four doctoral dissertations were completed between April 2004 and March 2006. 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 Care & Welfare I & II (2 credits, lecture)
- 5) Field Work for Health Administration (2 credits, practicum)
- 6) Health Promotion Sciences (1 credit, lecture)
- 7) Health Policy & Administration (2 credits, lecture)
- 8) Introduction to Health Economics (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, 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 Center for Biomedical Ethics and Law (CBEL) adjunct to the Department of Biomedical Ethics (<http://square.umin.ac.jp/CBEL/index.html>). The Center is funded by a ministry grant and is aimed to provide educational opportunities both to students and healthcare professionals outside the university. The Center holds 10 faculty positions and has started several public activities as of October 2003. In July 2003, an international collaboration resulted in a joint symposium with Case Western Reserve University (Clinical Bioethics: A Starting Point for Dialogue: A proposal for an Intercultural Exchange Between Japan and the United States).

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 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) Glycemic index as a tool for nutritional education
- 10) Dietary patterns among overweight men and women

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Health Sciences and Nursing

2. Nursing Sciences

Department of Nursing Administration / Advanced Clinical Nursing

Professor

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

Associate

Minako Sasaki, R.N., P.H.N., M.S.N.

Yukie Takemura, R.N., P.H.N., M.S.N.

Hideyuki Kobayashi, R.N., P.H.N., B.S.N.

Ayako Nagata, R.N., P.H.N., M.S.N.

Homepage <http://nurs-adm.m.u-tokyo.ac.jp/2004activities.htm>

Introduction and Organization

Nursing Administration department provides broad opportunities to learn about societal issues related to nursing education, nursing ethics, nursing administration, and 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, Lecturers)
Prof. Kanda and Affiliates
Exploration of political and administrative functional role in nursing. The course offers critical analysis of theories in nursing administration re-

lated 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, Lecturers)

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, Lecturers)

Prof. Kanda and Affiliates

An overview on models and theories in nursing, conceptual frameworks in nursing research, and clients' potential and actual physiological and psy-

chosocial responses to health problems. 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, Lecturers and practice)

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 Lecturers & practice)

Prof. Kanda and Affiliates

Students will understand the EMS (Emergency Medical Services) 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, Lecturers)

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, Lecturers)

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, Lecturers 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, practice)

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, Lecturers)

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, practice)

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.

8. Nursing Research (2 credits, Lecturers)

Prof. Kanda and Affiliates

This course offers examples of nursing research in various settings. Students will learn fundamentals of identifying problems for nursing research, measures taken, methods of quantitative/qualitative data collection and analysis, and reviewing research articles in nursing and health.

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 func-

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

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Department of Adult Nursing / Terminal and Long-term Care Nursing

Professor

Keiko Kazuma, R.N., Dr.Hlth.Sci.

Lecturer

Masako Kawa, R.N., Dr.Hlth.Sci.

Associate

Mitsunori Miyashita, R.N., M.Hlth.Sci.

Naomi Ito, R.N., Dr.Hlth.Sci.

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

Introduction and Organization

The Department of Adult Nursing / Terminal and Long-term 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.

Teaching activities

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 activities

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. It is our intention that these “research resources” will be widely utilized.

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 Focusing on the effects of drinking behavior on blood sugar control, we examined patients’ actual drinking behaviors and the related factors. We have developed a scale for eating behaviors associated with QOL, and investigated the QOL-associated factors. We have conducted a randomized clinical trial (RCT) for an

efficacy verification and economic evaluation of nursing support (individual nursing consultation) for the improvement of blood sugar control in collaboration with the Department of Diabetes and Metabolic Diseases at the University of Tokyo Hospital.

Inflammatory intestinal diseases: As ulcerative colitis (UC) and Crohn’s disease (CD) occur in young patients, and tend to relapse, long-term support for symptom control is required. We have developed a scale for assessing perceptions of daily life difficulties among UC patients, investigated the factors associated with the difficulties, and obtained suggestions for reducing such difficulties. Regarding CD, a one-year follow-up investigation was conducted with a focus on eating habits as a factor associated with relapse.

Bone and joint diseases: Regarding chronic rheumatoid arthritis, we investigated patients’ actual practice of exercising at home for symptom control and related factors. Regarding coxarthrosis (hip osteoarthritis), we described the QOL and difficulties experienced by patients who did not have operations, and investigated associated factors. Currently, we are conducting a survey on a wider range of subjects, including patients who had operations.

Physical activities of the elderly: We have developed and verified the validity and reliability of a Japanese version of a physical activity measurement scale that was developed in the United States. This study was conducted as a part of a Japan and Korea collaboration with contributions from members of the Seoul National University. Using this scale, the actual condition of physical activities of Japanese elderly was described, and related factors were identified.

2) Promotion of Patients’ Adaptation following Gastrointestinal Surgeries

Resection and reconstruction of gastrointestinal tracts are the main procedures used in cancer treatment, and are also used for other diseases, such as UC. A postoperative problem is the occurrence of physical impediments due to resection and reconstruction. The role of nurses includes supporting patients’ adaptive behaviors following a surgical procedure, and attempting to reduce the physical impediments the patients experience as much as possible.

We have developed a scale for assessing the life-stability perceptions of life stability in patients, who re-

quired a permanent stoma due to cancer. We suggested that the factors improving the perceptions of stability included “frequency of visits to stoma care outpatient clinics,” and “receiving support from nurses.” We are currently conducting a longitudinal study regarding the life-stability perceptions of individuals with stoma using this scale.

For patients with UC, during internal medical treatment, intake of lipids is limited. Since the limitation becomes unnecessary after total extirpation of the large intestine, the possibility of excess intake of lipids due to extreme changes in diet, and development of symptoms due to the surgery emerge; however, no investigation had been conducted on these issues. Therefore, we conducted a detailed patient survey regarding diet, postoperative symptoms, and coping behaviors (eating behaviors to reduce symptoms) following total extirpation of the large intestine.

3) 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 are currently conducting 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.

4) 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. We have performed a nation-wide survey, and have been con-

ducting educational activities regarding the promotion of nursing activity in outpatient care.

Regarding diabetes, which is predicted to rapidly increase in prevalence in the near future, we have clarified the current prevalence and problems regarding nursing support in outpatient clinics across Japan. We have also established protocols for consultation and guidance in outpatient care, and are promoting them for use in medical facilities across Japan.

Regarding HIV/AIDS, we have been promoting collaboration on nursing support for reinforcing patients' drug adherence with other facilities, and are attempting to spread these consultation and guidance activities across Japan.

5) Spiritual Pain of End-Stage Cancer Patients, and Spiritual Care

Although it has been said that end-stage cancer patients experience not only physical and psychological pain but also spiritual pain, this field has been ignored in modern medicine. We revealed the spiritual pain of Japanese end-stage cancer patients based on qualitative research. As the next step, we are attempting to develop nursing care for spiritual pain.

6) 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.

7) 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 transi-

tion 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.

8) 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. Our next step is to establish 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.

9) 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.

10) The Field of Basic Preparation for Nursing Research

We have been continuously conducting investigations on the tasks associated with nursing research methodology, and the nursing terms that are the foundation for the establishment of the field of nursing.

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Department of Family Nursing

Professor

Associate Professor

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

Lecturer

Akemi Yamazaki, R.N., R.M., P.H.N., Ph.D.

Associate

Noriko Matsui, P.H.N., M.H.S.,

Shiho Ozeki, R.N., R.M., P.H.N., M.S.

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

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 three faculty members; an associate professor, a lecturer and an associates.

Teaching activities

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

Research activities

Topics of our current research projects are as follows:

1. Psychological upset and psychological preparation of children undergoing minor surgery
2. Psychosocial factors related symptom management of children with cancer
3. Studies of Post Traumatic Stress Disorder (PTSD) and other late effects among survivors of childhood cancer
4. The development of an instrument measuring the quality of life of the caregivers for children with chronic illness
5. The development of an instrument measuring the quality of life for children
6. Qualitative research to explore childbearing family formation process
7. Postnatal depression and difficulties in childrearing
8. A study of mourning work in the family bereaved children

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Department of Community Health Nursing

Professor

Sachiyo Murashima, D.H.S., R.N., P.H.N.

Lecturer

Satoko Nagata, D.H.S., R.N., P.H.N.

Associate

Atsuko Taguchi, M.H.S., R.N., P.H.N.

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

Introduction and Organization

Department of Community Health Nursing was established in June 1992. At present, there are three faculty members introduced above and 12 graduate course students (5 in master course, 7 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) Community Health Nursing Practice (3 credits, practice)
This program is intended to understand the system of health promotion and prevention by attending the actual community health nursing ac-

tivities. Students are expected to realize the principle and the common technique of community health nursing activities by observing the activities of public health nurses.

- 3) Geriatric Community Health Nursing (2 credits, lectures)
The aim of this class is to have a deep understanding of the social context around the elderly and the medical, health and welfare system. Also, students attend the nursing practice at a visiting nurse station to understand the home care.
- 4) 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
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 on home care and methodology of qualitative research for

community health nursing.

- 3) Advanced Community Health Nursing Seminar I, II (4 credits)

Student participate one of the projects which encourage their study and promote their ability.

- 4) Field Work on Advanced Community Health Nursing I, II (4 credits)

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. 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

For the purpose of health maintenance and improvement of the community residents, public health nurses provide services (i.e. "personal support") to each resident and family with health problems. On the other hand, they play a role to develop new services to provide more effective and efficient support to more residents with same kinds of problems and influence the administrative decision. These activities are called "development of program," which lately had been recognized as an important function of public health nurses. We are conducting researches to clarify the techniques used by the public health nurse's in program development.

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.

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. Expansion and enforcement of visiting nursing activities

We are conducting researches to develop and expand the field of visiting nurse services, through the model projects to deliver the visiting nurse services to group-homes for elderly, and to find and encourage the role of visiting nurse service stations in rural and remote areas.

5. Support for families with babies and children

We are conducting researches covering two fields, community health and occupational health. For example, we compare the work-family conflicts of working mothers and fathers with small children in order to reduce their stress and burden. Also, the network for childrearing was investigated to avoid child abuse.

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Department of Psychiatric Nursing

Professor

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

Lecturer

Yuki Miyamoto, R.N., P.H.N., P.S.W., Ph.D.

Homepage <http://plaza.umin.ac.jp/heart/>

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, 5 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.

Teaching activities

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 relevant English articles are introduced by graduate students. Also, prominent guest speakers give lectures from time to time in this seminar.

Research activities

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; and patient satisfaction with psychiatric services. We are conducting studies in collaboration with researchers in other institutions and universities.

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Department of Midwifery and Women's Health

Professor

Satiyo Murashima, Ph.D., R.N., P.H.N.
(Concurrent office: Community Health Nursing)

Lecturer

Megmi Haruna, Ph.D., R.N., R.M., P.H.N.
Ryoko Murayama, MS., R.N., R.M.

Associate

Etsuko Watanabe, MS., R.N., R.M., P.H.N.

Homepage <http://park.itc.u-tokyo.ac.jp/midwifery/index.html>

Introduction and Organization

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

Currently, it has 4 faculty members introduced above and 6 part-time lecturers, 3 graduate students (2 in master course, 1 in doctoral course), and one research student.

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)

Research activities

Our research activities focus on maternal-child health care as well as health promotion and quality of life of women in each life cycle.

Current research projects are as follows.

- 1) Life style and oxidative stress during pregnancy
- 2) Maternal body composition during pregnancy
- 3) Nutrition and weight management during pregnancy and postpartum
- 4) Quality of sleep and sleeping posture of women
- 5) Promotion of women's health care during postpartum.

- 6) Application of the ICF (International Classification of Functioning Disability and Health) to an assessment of quality of life among pregnant women

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Department of Gerontological Nursing

Professor

Hiromi Sanada, R.N., P.H.N., WOCN., Ph.D.

Lecturer

Etsuko Tadaka, R.N., P.H.N., Ph.D.

Associate

Atsuko Kitagawa, R.N., M.S.N.

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

Introduction and Organization

The Department of Gerontological Nursing is the newest department of the Health Sciences and Nursing Division of the Graduate School of Medicine, The University of Tokyo, which was established in June 2003, and currently it has the members; a professor, a lecturer, an associate, five adjunctive lecturers, three graduate students and three research students. Our main activity policy involves the "Practice and Development of Gerontological Nursing Based on Evidence" We wish to create a society that respects the beauty of aging and recognizes it to be a joyful process in life.

Teaching activities

1. Undergraduate course

1) Gerontological Nursing (4 credits, Theory)

As for undergraduate education, our department takes a part in systemic lectures of Gerontological Nursing for the 3rd to 4th year students. In the 3rd year, the goal is set to comprehend the physical, psychological and social characteristics of the elderly population, and the main contents in 2004-2005 were as follows; a) Introduction to Gerontological Nursing, b) Physical, psychological and social characteristics of the elderly, c) Legal and policy for the elderly, d) Health assess-

ment and care approach of the healthy elderly, e) Features of health and illness in the elderly, and f) Feeding and swallowing difficulty in the elderly. In the 4th year, the goal is set to understand basic knowledge about concept, pathology, diagnosis, treatment and care of major geriatric syndrome, and the main contents in 2004-2005 were as follows; a) Pharmacologic management in the elderly, b) Rehabilitative approach in the elderly, c) Age-related changes in the physiologic system, d) Respiratory disorders of the elderly, e) Urinary disorders of the elderly, f) cognitive disorders of the elderly, g) cardiovascular disorders of the elderly, h) Osteoporosis of the elderly, i) Physical assessment of the elderly, and j) Comprehensive geriatrics assessment and care of the elderly with dementia 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 (3 credits, Theory)

The program goal is set to develop knowledge and skills of the professional nursing care for the elderly, especially for the elderly with dementia, in a clinical setting. The program was supported by The Tokyo Musashino Hospital Affiliated with a Juridical Foundation, The Institute of Clinical Psychiatry in 2004-2005.

3) Bachelor's thesis

(1) Research themes in 2004 were as follows:

'The prevention of heel pressure ulcers: Effect of vibration on blood flow', 'The preventable pressure ulcers and The unpreventable pressure ulcers -Wound Ostomy and Continence Nurse's opinion-'

(2) Research themes in 2005 were as follows:

'Developing the air mattress with a pressure monitoring sensor: Validity test of the sensing property and determination of the sensing area', 'Vibration increases the skin blood flow in the auricle: Investigation using mouse model for visualizing the microcirculation', 'Depressive state of the elderly living alone in an urban area'

2. Graduate course

1) Gerontological Nursing I (2credits, Theory)

2) Gerontological Nursing II (2credits, Theory)

The course program focuses on understanding and development of the practice, research, education, and perspectives in advanced gerontological nursing. Gerontological Nursing I offers review and critical analysis of recent world-wide researches around gerontological nursing. The main research in 2004 was 'Assessing care of vulnerable elders: ACOVE project' which was organized by RAND, USA (Wenger NS., et al., 2001) and the main research in 2005 was 'The Nun Study' which was organized by NIH, USA (Snowdon D., et al., 2003). Gerontological Nursing II provide lectures and discussion about the recent topics around gerontological nursing, and main themes in 2004-2005 were as follows; a)Introduction to Geriatrics syndrome, b)Accidental fall in the elderly, c)Homebound in the elderly, d)Dementia from the inside, e)Needs at natural disaster in the elderly, f)Social support in the elderly, g)Feeding and swallowing difficulty in the elderly, h)Pressure ulcer in the elderly.

3) Master's thesis

A research theme in 2005 was as follows; 'Bilateral Comparison Study to Evaluate a New Pressure Ulcer Preventive Dressing Containing Ceramide 2 with a Low Friction Outer Layer'

Research activities

1. Activity policy

In Our main activity policy involves the "Practice

and Development of Gerontological Nursing Based on Evidence" where we are striving to develop new nursing techniques and instruments to improve the prediction, prevention, diagnosis and treatment of the elderly with issues of geriatric syndrome, specifically pressure ulcers, incontinence, malnutrition, pain, depression, and dementia. Almost researches are conducted under industry-academia cooperation. We hope to increase physical activity and enhance self-esteem of the elderly in order to maintain their independent lifestyles through the researches.

2. Research fields and themes

- 1) Development of new techniques and instruments for wound care management for the elderly
 - Risk assessment
 - Preventive care
 - Malnutrition
 - Skin care
 - Wound management
- 2) Development of care program and system for the elderly
 - Health promotion program for the healthy elderly/ the elderly living alone
 - Preventive approach in long term care for the frail elderly
 - Therapeutic care program for the elderly with dementia
 - Reminiscence group care program for the elderly

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International Health

1. International Social Medicine

Department of Health Policy and Planning

Associate Professor

Chushi Kuroiwa, M.D., Ph.D.

Associate

Ali Moazzam

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

Introduction and Organization

Our planet has faced enormous challenges such as famine, scarcity of clean water, growing number of population, and environment degradation, which have serious impacts on our health. International society had hoped that the end of the cold war would prove to be a turning point; however, globalization has been gaining huge power, showing some negative aspects as well as benefits. The poor have been pushed farther away from reaping its benefits. Global warming might cause frequent storms, floods, receding glaciers, and arising sea level; such climate change pose worrying health risks.

Industrialized countries have developed sophisticated health policies on behalf of developing countries, yet many issues remain when considering the sustainability of such projects. As one of the leading universities in Asia, our aim is to reveal the hidden realities of health policy, and provide clues to improving health situation in the developing countries through understanding the existing health system and respecting the indigenous culture of the country.

Teaching activities

There are the following academic courses:

- 1) Master Degree (Health Science) : 2 years
- 2) Doctoral Degree (Health Science) : 3 years

We accept any students who have bachelor degrees,

but preferably those who have some experience of working in developing countries and good English ability. We have network with IMCJ (International Medical Center of Japan), which operate various international projects overseas.

The following are the main topics covered in the academic year 2005;

1. Introduction, health situation in the country with IMR 150, and community based health care for children: PHC, IMCI
2. The history of ODA and international health: driving force of development and another approach
3. Role of NPO/NGO in International Health
4. Policy Advocacy and Roles of Civil Society Actors – Applicability of Lessons Learnt from ODA Reform for Health Policies
5. Japanese ODA, International Health, ODA Evaluation and monitoring
6. Public health response to bio-terrorism / Role of international health by PKO
7. Green revolution
8. EPI (expanded programme on immunization) & global eradication of infectious disease
9. Health Policy, an introduction to process and power
11. Introduction to health systems / Health planning cycle / Health sector reforms in recent times
12. PHC and community participation

13. Malaria control and health policy
14. TB control and PHC, ARI
15. Infectious disease surveillance in Japan
16. Nutrition programme and health policy

Department meeting

Department meeting is held every Monday (10:00am-12:00pm), which is divided into two sessions; 1) Journal reading and 2) Presentation of research progress. Presentations of field experience are given on ad hoc basis by guest speakers (e.g. IMCJ, JICA experts, NPO/NGO, WHO staff etc.), visiting researchers, students or department staff.

Below are the presentations given by guest speakers in 2004;

- Access to safe water in developing countries
 - Japan disaster relief
 - Aid coordination & harmonization: Case study in Vietnam
 - A brief overview of international health education programs
 - Participatory Evaluation
 - Human resource development for maternal health in post-conflict countries
 - Maternal health in Republic of Armenia
 - Development study in health sector (JICA)
 - Geographical Information Science Approach for health policy and planning
 - Reaching the poorest and making the world equitable
- etc...

Research activities

1. Evaluation of ODA (official development assistance) and international health policy
2. Health system improvement in developing countries
3. EPI and vaccine preventable diseases in developing countries
4. IMCI (Integrated Management of Childhood Illness) in developing countries
5. Community PHC: malaria prevention; hygiene behavior in developing countries
6. HIV/AIDS, STIs control and prevention
7. Injury epidemiology in developing countries
8. Asthma epidemiology and risk factors in developing countries
9. Reproductive health in developing countries
10. Medical wastes in developing countries

Reference (April 2004 – March 2005)

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Department of International Community Health

Professor

Susumu Wakai, MD, PhD

Lecturer

Masamine Jimba, MD, PhD, MPH

Associate

Shinji Nakahara, MD

Masao Ichikawa, PhD, MPH

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

Introduction and Organization

The department of international community health has been headed by three professors since 1993; Professors Gen Oi (1993-1996), Som-Arch Wongkhomthorn (1996-1999), and Susumu Wakai (1999-2005).

The mission of the department is to seek equity and social justice in health within and across the nations. Our aim is to bring together the clinical, public health and social science research to address the broad issues of public health in the world. The goals are to:

1. Investigate how to improve health status of the most vulnerable people, in particular, in developing countries,
2. Undertake research on the influences of 'globalization' and 'free market' system on health and social development,
3. Investigate the mechanisms to reduce inequalities between and within nations on health and development.

The organization of the department is as follows: Professor (1), Lecturer (1), Associate (2), Visiting Lecturer (6), PhD course student (9), Master course student (11), Visiting fellow (2), Visiting scientist (16).

International Cooperation Activities

Our department has conducted a variety of international cooperation activities through JICA and non-governmental organizations. The target countries have been Nicaragua, Lao PDR, Cambodia, Thailand, Vietnam, and Myanmar. In particular in Lao PDR, we have worked together with the Ministries of Health and Education as well as WHO, UNESCO and completed a comprehensive school health policy and its guideline at a national level.

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) What is international health? 2) Health promotion in developing

countries, 3) Health economics, 4) Research ethics, 5) Project management, 6) 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, leprosy, etc. The target countries have been those in South Asia, South East Asia and Nicaragua. The outcomes of our research are listed in the next section.

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International Health

2. International Biomedical Sciences

Department of Human Genetics

Professor

Katsushi Tokunaga, D.Sc.

Associate Professor

Naoyuki Tsuchiya, M.D., D.M.Sc.

Research Associate

Jun Ohashi, D.H.Sc.

Hiroko Miyadera, D.M.Sc.

Homepage <http://www.sih.m.u-tokyo.ac.jp/departments-E.html>

Introduction and Organization

The Department of Human Genetics was established in 1992. Currently, the department has one professor, one associate professor, two research associates, 19 graduate students, 6 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 analy-

ses, as well as gene expression profiling, to better understand the genetic background of a variety of complex diseases, especially autoimmune diseases, infectious diseases and sleep disorders.

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.

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Department of Developmental Medical Sciences

Professor

Hiroshi Ushijima, M.D., Ph.D.

Associate Professor

Hideoki Fukuoka, M.D., Ph.D.

Associate

Masaaki Oda, Ph.D.,

Shoko Okitsu, Ph.D.

Homepage

Introduction and Organization

From the scholarly point of view, the history of maternal and child health, which is the previous name of our department, has started recently. As far as Japan is concerned, our department, which was established a few decades ago, is the very first one. Maternal and child health involves all activities conducting to maintain and promote psychological and physiological health of mothers and children. The field of maternal and child health covers (1) countermeasure for infectious diseases, (2) maternal and child nutrition, (3) prevention of diseases, and (4) protection of mothers and children from environmental unhealthy factors.

Under the study of maternal and child health, medical care and welfare are also considered to compensate diseases and abnormalities that cannot be prevented. Maternal and child health services in communities are the responsibilities of administration, however, optimal policy making and technological development for ideal services must fall within the scope of researches in the study of maternal and child health.

Since 1998, the department changed to a new name, Developmental Medical Sciences for the purpose of expansion of research and teaching activities. Aging, human and environment, and their related items are newly added to our theme.

Teaching activities

1. Undergraduate course, Faculty of Medicine, School of Health Science and Nursing (Lectures: all staff, 150 hr; Laboratory course: 50 hr)
 - 1) Maternal and child health
 - 2) Growth and development
 - 3) Aging
 - 4) School health
 - 5) Molecular medicine for maternal and child health
 - 6) Virology
 - 7) Immunology
 - 8) Diseases in maternity cases and in children
 - 9) Human embryology
 - 10) Special topics in maternity cases and children
 - 11) Practicing how to care diseases in maternity cases and in children
 - 12) Sexual medicine and sexual education
2. Graduate course, Faculty of Medicine, School of International Health Science (Lecture; 90 hr)
 - 1) Child health
 - 2) Maternal health
 - 3) Growth and development

In addition to lectures and laboratory courses by our own staff, special lectures are given by the experts both inside and outside the University.

Research activities

- (1) Community health services for mothers and children
- (2) Studies on molecular epidemiology of infection
- (3) Studies on prenatal and perinatal behavior in relation to child health
- (4) Effects of high-rise living on physical and mental development of children.
- (5) Biochemical study of post-translational modification of glycoprotein hormones
- (6) Calcium and bone metabolism in puberty, during pregnancy and puerperium and in the post-menopausal state
- (7) Research on statistical evaluation, sex education and health promotion in maternal and child health
- (8) Immunological and molecular immunogenetical approach to bacteria
- (9) Brain and development
- (10) Biochemical analysis of immobilization on calcium and bone metabolism
- (11) Gene expression of biologically active peptide in the human placenta
- (12) Antiviral agents and their mechanisms
- (13) Development of new diagnosis
- (14) HIV
- (15) Research on Children's Environments
- (16) Mother to Child Transmission of Infection
- (17) Fetal origins of adult disease

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Department of Human Ecology

Professor

Chiho WATANABE, D. Hlth Sc.

Associate Professor

Masahiro UMEZAKI, Ph.D.

Associate

Taro YAMAUCHI, Ph.D.

Hana SHIMIZU, Ph.D.

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

Introduction and Organization

Ex-Professor Ryutaro Ohtsuka retired in March, 2005, who was succeeded by current Professor Watanabe in April, 2005. Dr. Shimizu (associate) and Dr. Umezaki (associate professor) joined in May and August, 2005, respectively. Together with Dr. Yamauchi (associate), we have four research/teaching faculties since then. Apart from the faculty staffs, a secretary (Ms. Tamami AOYAGI), five doctoral candidates (including two foreign students), five master course students (including two foreign students), and two research fellows are working in the department. There are nine extra-university lecturers delivering lectures in either graduate or undergraduate courses.

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 pressing 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 fell into the field of “Environmental Health” and/or “Population biology [of human]”, and we utilized both fieldwork and experimental approach. Most of our study fields were 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 relatively sensitive to these chemical substances, we focused 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 of so called endocrine disrupting chemicals. 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, and demonstration of developmental neurotoxicity of low-dose of cadmium. Another experimental study regarding the interaction between selenium and arsenic was conducted, hinted by our field study finding; effects of thyroid hormones as well as mutual modification of the kinetics were found.

2. Water and air quality and health in developing countries:

In many Asian and Latin American countries, pollution of groundwater has been a serious problem for health. We have conducted surveys in Bangladesh, where a large-scale groundwater contamination by arsenic poses serious threat. We have extended this survey to Nepal, confirming our previous findings of males' susceptibility to arsenic, and demonstrated the mutual relationship between malnutrition and arsenic toxicity.

In Indonesia, we have started a study on water pollution by pesticides, metals, and others, the final goal of which is to evaluate the effects of contamination on children's health. A survey of water quality has been conducted as the first step.

Air pollution in the developing countries is another vexing environmental issue, especially in Asian urban areas. Body burden of lead (Pb) in bus terminal workers in an Indonesian city has been examined; possible

modification of body burden by nutritional status was shown.

3. Studies on nutrition, growth, and physical activities (energetics) in developing countries:

Nutrition is one of the fundamental requirement for health and is especially important in developing countries.

In rural Bangladesh, food consumption, nutritional status, and activity of the villagers were examined; distinct gender-related difference was found.

In rural Western Java, Indonesia, the relationship between the nutritional status during the preadolescent period and biological parameters at birth were analyzed. In Tonga, where the prevalence of obesity is high, anthropometry was conducted for adolescent girls, and factors associated with obesity were identified.

In the schoolchildren of rural China, prevalence of the infection with schistosomiasis was examined and the relative importance of the parasite infection and nutritional status for the physical growth of the children was evaluated.

Physical activity and energetics are important not only from the viewpoint of Human Ecology but also from the prevention of lifestyle-related diseases. Our focus has been on the energetics of the people living in their daily life. In Papua New Guinea, it was examined how the domestic migration from rural villages to urban area changed the physical activity of the people. Also, the energetics of Sumo-wrestlers were characterized.

4. 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 were made in China as well as Solomon Islands. 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, Geographical Information System

(GIS)/GPS was used for analyzing the relationship between the subsistence transition and land-use.

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Department of Biomedical Chemistry

Professor

Kiyoshi Kita, Ph.D.

Lecturer

Yoh-ichi Watanabe, Ph.D.

Associate

Kimitoshi Sakamoto, Ph.D.,

Shigeo Yoshinari, Ph.D.

Homepage<http://www.sih.m.u-tokyo.ac.jp/departments-J.html#Anchor-33869>

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 re-named on April 1st, 1996 to The Department of Biomedical Chemistry as newly affiliating with Biomedical Science Division of International Health, Graduate School of Medicine, The University of Tokyo. Prof. Kita has moved from The Institute of Medical Science, The University of Tokyo on March 1st, 1998.

Teaching activities

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

Graduate Course: Biochemistry and Nutrition I, II

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

Undergraduate Course: Biochemistry, Molecular Biology, Laboratory Method in Health Science, Physiological Chemistry, Nutrition, Medical Chemistry, Practice on Medical Chemistry, Parasitology.

Research activities

Energy metabolism is essential for the survival, continued growth and reproduction of living organisms. From the standpoint of biological adaptation, we have been studying on the molecular mechanism of energy transducing systems such as mitochondrial and bacterial respiratory chain. In addition, we are interested in the basic biological reactions such as protein synthesis. Our research have been focusing on

I. Human mitochondria

- 1) succinate-ubiquinone reductase
- 2) mitochondrial myopathy

II. *Ascaris suum* and *Caenorhabditis elegans*

- 1) molecular mechanism of adaptation to low oxygen tension (regulation of gene expression of mitochondrial proteins)
- 2) mitochondrial fumarate reductase (structure function relationship, enzyme evolution)

- 3) *C. elegans* as a model system of parasitic nematode (expression of foreign genes or cDNAs, gene knockout)

III. Parasitic protozoa (*Plasmodium falciparum*, *Trypanosoma brucei*, *Trypanosoma cruzi*, *Cryptosporidium*)

- 1) characterization of mitochondria as a target for the chemotherapy
- 2) molecular biology of mitochondrial DNA
- 3) structure based drug design (SBDD)

IV. Protein synthesis

- 1) Mitochondrial protein synthesis
- 2) Biogenesis of cytoplasmic ribosomes

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University Hospital

Clinical Divisions

General Medicine

Professor

Yasuyoshi Ouchi, M.D., Ph.D.

Homepage

Organization

the setting of primary care with guidance by our staff.

The Department of General Medicine started as an outpatient primary care at the reorganization of Department of Internal Medicine in 1994. Our department functions as a primary care unit, and new patients with medical problems first seen and undergo screening examinations by the staffs in this department. Once diagnosis is made, the patients are referred to appropriate specialists. Our department consists of one professor (Chairman of Internal Medicine), one lecturer and many other staffs nominated by subspecialty departments of Internal Medicine. Most of them rotate between General Medicine and subspecialty with the duty of General Medicine for 1-2 months a year. A few staffs practice oriental medicine.

Activities

Three booths in outpatient clinic are allocated to our department every day. New patients without appointment or referral letters first visit our department. Most of the acute illnesses and common diseases are tentatively treated or referred to the specialists if needed. In the case of chronic diseases, they will be referred to the specialists after appropriate screening and evaluation of the morbidity. We see 70-80 such patients every day, and the total number of outpatients in 2005 was about 20,000. At present, our department is not provided with ward. Therefore, the patients who needed hospitalization are referred to relevant subspecialty. In addition to the management of outpatients, we provide an opportunity for medical students and junior residents to learn the skill of medical interview, physical examination, medical planning, diagnosis, treatment and so on under

General Surgery

Professor

Masatoshi Makuuchi, MD

Homepage

Organization

The Department of General Surgery started as an outpatient primary care unit in 1994. The Department serves as a screening centers for the patients with surgical problems first seen. Once diagnosis is made, the patients are referred to appropriate specialists. Our department consists of one professor and many other staffs nominated by sub-speciality departments of Surgery. Most of them rotate between General Surgery and sub-speciality with the duty of General Surgery for 2-3 months a year.

Activities

Three booths in outpatient clinic are allocated to our Department every week day. New patients without appointments or referral letters first visit our Department. Acute surgical diseases are initially treated at our Department or referred to specialist if needed. Most of the patients with diseases that needs operation will be referred to specialists after appropriated screening. We see 20-30 such patients every day and the total number of outpatients per year is appropriately 5000. At present, our department is not provided with ward. The patients who need hospitalization are referred to relevant sub-speciality.

University Hospital

Central Clinical Facilities

Clinical Laboratory Center

Professor

Yutaka Yatomi, M.D.

Associate Professor

Hitoshi Ikeda, M.D.

Lecturer

Katsu Takenaka, M.D.,

Daiya Takai, M.D.,

Tatsuo Shimosawa, M.D.

Makoto Yumoto, M.D.

Associate

Katsumi Higashi, Ph.D.,

Aya Ebihara, M.D.,

Makoto Kaneko, M.D.

Chief Technologist

Minoru Toduka, Ph.D.

(As of March, 2006)

Homepage <http://www.cc.h.u-tokyo.ac.jp/mulins/kensa/index.htm>

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 Administration Section

This Section has been newly established and deals with management issues in Clinical Laboratory Center.

The 1st Section

This section deals mainly with the maintenance of

laboratory system, blood and urine sampling, and urinalysis. In 2004, 185,000 outpatient blood sampling were performed while 73,000 urine samples were analyzed, in this section.

The 2nd Section

This section deals with clinical biochemistry and immuno-serology tests. In 2004, over 250,000 serum enzyme tests (such as AST and ALT), and 200,000 CRP tests were performed. On the other hand, 37,000 STS and 28,000 CEA tests were performed, which is just a few examples of the tests performed in the last year.

The 3rd Section

This section deals with hematology and DM-related tests, and gene analysis tests. In 2004, 280,000 samples were examined for complete blood cell counts, while 1,600 cell surface marker analysis and 100,000 prothrombin time, 65,000 fibrinogen, 90,000 glucose, and 61,000 HbA1C tests were performed. As for genetic tests, 450 leukemia-related gene tests and 4,000

HCV-RNA tests were performed.

The 4th Section

This section deals with physiological tests, including circulatory, pulmonary, and neuromuscular function ones. In 2004, 26,000 ECG, 7,200 pulmonary function tests, 7,900 echocardiography tests, 9,600 abdominal echography tests, and 1,700 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. Blood glucose measurements and abdominal echography tests are also performed in the ward by technologists belonging to this section. 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) hematological analysis, ii) cell surface analysis using flow cytometry, iii) analysis of life-style involvement in clinical laboratory data, iv) bioactive lipids, iv) hormones, including FGF-23 and adrenomedullin, v) analysis of cardiac functions using ultrasound, vi) the influence of diesel exhaust particles on respiratory functions, and vii) analysis of brain functions using magnetoencephalography. The improvement of the current laboratory test methods is

constantly performed in all laboratory sections.

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Surgical Center

Director (Professor)

Masatoshi Makuuchi M.D., Ph.D.

Associate Professor

Yoshikazu Mimura, M.D., Ph.D.

Yushi Uetera, M.D., Ph.D.

Lecturer

Nobusuke Ohara, M.D., Ph.D.

Ryoji Fukushima, M.D., Ph.D.

Mieko Chinzei, M.D., Ph.D.

Associate

Toshihiko Obayashi, M.D., Ph.D.

Saito Yuhei, Ph.D.

Chizuru Komori, M.D., Ph.D.

Homepage

Introduction and Organization

Operating rooms were centralized as a surgical center for the first time in Japan, in the University of Tokyo 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. The new surgical center has 14 operating rooms, one of which is a bio-clean room. The administration staffs consist of 5 doctors, 54 nurses, 6 technical officials, 6 temporary employees. Our surgical center affords services to 18 clinical departments of our hospital. In 2004, 7546 operations were performed in our surgical center including 1096 emergency operations.

In July 2001, the branch hospital of our university located in Mejiro was closed and joined to our University Hospital located in Hongo. Furthermore, a new ward building was opened in October 2001. Then, the number of operations has been remarkably increased and reached to more than 7500. Another new central building including new operating rooms is now constructing. Our hospital is in the state of chronic shortage

of available operating rooms.

Two new operating rooms are tentatively prepared to overcome the increase in operations. One operating room is prepared in the ICU, CCU, HCU floor of the new ward building and the other is prepared in the outpatient clinic of the orthopedic surgery. The operating room in the outpatient clinic is also used for the short-stay and day surgery procedures in orthopedics.

Another effort was made to increase the availability of the operating rooms in light of the efficient management of the surgical center. Until September 2001, nine operating rooms were used daily for the elective operations on the average. However, 12 operating rooms have been used daily for the elective operations since October 2001. As a result, the number of operations has been increasing remarkably since October 2001. We had 8013 operations in 2005 which is 1.4 times of those in 2001.

Activities of our surgical center

Activities of our surgical center encompass teaching

activities, research activities and management of the surgical center.

Management of the surgical center

All operations of in-patients are performed in 14 operating rooms of the surgical center. In addition, one operating room is also used for the short-stay and day surgery procedures in orthopedics. The number of operations is increasing annually. As mentioned before, there were 7546 operations in 2004, including 1096 emergency cases.

However, the total number of operations has not increased between 1999 and 2000 apparently, partly because of the shortage in the number of operating rooms and nursing staffs. There is also 5 to 18% annual increase over these 4 years in the number of operated patients with either unknown results or positive results in the microbiological tests regarding such as lens, tuberculosis, MRSA, pseudomonas aeruginosa, HBV, HCV and HIV.

Computer system has been introduced in the management of information in the surgical center. In May 1999, on-line computer system was introduced to ordering system for the planned and emergency operations. Namely, all operations have been ordered through the computer terminal installed at each clinical department since May 1999. Furthermore, the computer system has also been introduced to manage the postoperative information in the surgical center since March 2000.

To encourage the efficient management of operating rooms, the information has been disclosed on the hospital computer network since May 1997, regarding if there are any operating rooms without any planned operations on the following day. Furthermore, since November 2000, it is disclosed on the hospital computer network how each clinical department plans to use the operating rooms on the following week in order to use the available operating rooms efficiently.

Digitalized visual information such as photographs of operative fields and resected organs has been distributed to each clinical department through hospital computer network system since February 1997. Moreover, real-time monitoring visual information of the operative fields has been distributed to each clinical department on the hospital computer network since June 1999.

Since the new ward building began to be used in October 2001, SPD and progressive patient care system have been introduced in the management of our hospital. SPD system was introduced in the management of the surgical center in September 2002.

Recent trend is a remarkable increase of complex procedures such as in transplantation surgery, microvascular surgery, cardiovascular surgery, minimally invasive surgery and orthopedic surgery. In addition, none-human implants such as vascular prosthesis, joint prosthesis and intraocular lenses have come to be used frequently.

Furthermore, advanced techniques have been employed in the operating theatres. They are navigation surgery in neurosurgical, orthopedic and ENT (ear, nose and throat) operations, treatment of thoracic aortic aneurysms using stent devices under fluoroscopic monitoring. In addition, application of minimally invasive surgery such as MIDCAB operations are performed in the aortocoronary bypass procedures as well as a heart-port surgery in the correction of heart anomalies such as ASD and VSD. In addition, transplantation operations and intraoperative three-dimensional echosonography 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 lectured to all health care workers in the surgical center.

It is considered that the number of immunocompromised hosts and complex surgical procedures will increase remarkably in the perioperative services of the surgical center. Therefore, it is mandatory to improve the quality and management of the surgical center in the twenty-first century. As a result, it is considered that the role of surgical center is extremely important in health care services of hospital.

Teaching activities

Lectures to the undergraduates and postgraduates are as follows: aseptic techniques, sterilization methods, disinfection methods, prevention of perioperative infections, humoral and cellular responses to trauma and

shock, training of handwashing 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.

It is one of the recent trends in the surgical center that innovative surgical instruments and medical devices are 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. Advanced technologies are lectured to the surgeons, nursing staffs and medical electronics engineers so that they understand how to use them correctly.

Lectures to 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 on aseptic techniques, de-contamination methods, disinfection methods, sterilization methods, prevention of perioperative infections, and training of hand-washing 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 abilities so that they can afford satisfactory nursing services 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.

Lectures to the non-nursing staffs such as technical officials and temporary employees are 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 performed to senior technical officials and temporary employees to upgrade their technical knowledge and skills.

Research activities

- 1) Introduction of aseptic environment in the operating theaters
- 2) Development of new sterilization methods
- 3) International standardization of sterilization methods
- 4) Perioperative infection control of patients undergoing operations and prevention of occupational infection of medical staffs working in the surgical center
- 5) Improvement of cost-effectiveness in the management of surgical center
- 6) Precautions of accidental troubles in the handling surgical instruments and medical devices
- 7) Improvement of cost-effectiveness in sterilization and preservation of medical instruments
- 8) Cost-effectiveness analysis of disposable and reusable surgical instruments
- 9) Development of new surgical instruments and medical devices
- 10) Computer aided surgery
- 11) Intra-operative radiation therapy
- 12) Surgical treatment on the basis of molecular biology
- 13) Inter-hospital visual communications via satellite system
- 14) International comparison of effectiveness in the management of surgical center
- 15) Computer aided anesthesia
- 16) Three dimensional processing of visual information
- 17) Improvement of minimally invasive surgery and microsurgery

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Department of Clinical Radiology

Professor (department manager)

Kuni Ohtomo, M.D.,Ph.D.

Lecturer (vice manager)

Tomohiko Masumoto, M.D.,Ph.D.

Associate

Shinichi Inoh, M.D.

Homepage <http://www.ut-radiology.umin.jp/>

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 and the 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. Parts of the diagnostic activities are done at the MR building, the operation rooms, 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 basement of the inpatient building B. 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. 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: 3D-conformation therapy, clinical PET, multi-detector row CT, interventional 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. One hundred and fifty CT examinations are performed using four MDCT scanners each day. Interventional procedure such as percutaneous biopsy and abscess drainage are also done by CT guidance. About forty MR examinations are done using two 1.5-Tesla and one 0.3-Tesla machines every day. About six angiographies, most of which are interventional procedures including arterial embolization, arterial infusion therapy, arterial infusion port placement, angioplasty, and TIPS, 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.

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 anatomo-functional 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

Yuji Taketani

Homepage

Organization

The Delivery Unit of the University of Tokyo Hospital is organized by one professor, one associate, and 5-10 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 from April 2005 to March 2006 is 557, whereas that from April 2004 to March 2005 is 514.

Recently cases of obstetrical emergencies like abruptio placentae, eclampsia and uterine ruptures transported from neighboring hospitals have been increasing. These patients are treated by two or three doctors and three midwives in charge under round-the-clock system. Our service is an important part of Tokyo Metropolitan Service System for Maternal Welfare and Perinatal Medicine.

References from April 2004 to March 2006

[See Department of Perinatal Medicine.]

Central Rehabilitation Service

Professor

Fumio ETO, M.D., Ph.D.

Associate

Naoyuki MIYAKE, M.D.,
Ikuko SAOTOME, M.D., Ph.D.

Tosikazu Furukawa, M.D.

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

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 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 (April, 2005) our department consists of 4 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 two occupational therapists work for the psychiatric rehabilitation. A part-time clerk is also working for administration section concerning medical rehabilitation service.

Clinical, teaching and research activities

A professor of the department of rehabilitation medicine holds an additional post of the director of the central rehabilitation service department. Both departments are united and engage in clinical, teaching and research activities. We have no own ward for the patients in medical rehabilitation but accept about 1,000 new inpatient referrals every year from other departments of the university hospital. Approximately 200 inpatients are under care of our rehabilitation service everyday. At outpatient clinic ten to twelve patients visit us everyday mainly as follow-up cases.

As for the characteristic of our patients, the number of severely deconditioned patients with high-risk factor for physical training has recently increased. They suffer from remarked disabilities with underlying disorders such as cancer, cardiac and pulmonary failure, renal and hepatic insufficiency, and various degenerative diseases. The establishment of a new therapeutic regime for these patients with difficult complications and comorbidity may be urgent. Most of them cannot come to the rehabilitation room because of their severe medical condition. Therefore, the therapists have to visit the ward and to conduct the rehabilitation trainings for them.

Concerning the rehabilitation of the mental disorders, two occupational therapists specifically engage in treatment activities. The occupational therapy in the psychiatry ward and large-scale day-hospital has been

allotted in cooperation with the psychiatry department staffs. About 40 people, mostly with schizophrenia, are registered in day hospital service. They are called members and come to the hospital since Monday to Friday and participate in various activities.

Acupuncture therapy is a traditional medical activity of long history and a unique section in Japanese university hospital. This is nowadays the most popular complementary and alternative medicine and may be expected its usefulness in rehabilitation treatment. We have provided an acupuncture and moxibustion treatment for many patients with pain syndrome and myofascitis at the University of Tokyo hospital for dozens of years, but have been not able to contribute to a hospital income because of the limitation on insurance medical care. Then, as a result of having reviewed measures in this country, we get possible to charge therapeutic fee as free medical care since April, 2005.

As for teaching activities, we have provided a three-day clinical presentation for small group (so-called bedside learning) of 5th year students on every other Wednesday to Friday. All the medical students see a few patients and also experience orthoses, prostheses, mobility aids, wheel chairs and others. We also have accepted co-medical students for clerkship and internship as second, third and fourth year curriculum from several PT and OT training schools.

Research Activities are almost same as those in the department of rehabilitation medicine. Our co-medical staffs are also interested in research activity. The research fields done by the present staffs are as follows:

- (1) gait analysis for evaluation of prosthesis and orthosis for various limb amputees, rheumatoid, post-stroke hemiplegic patients.
- (2) biomechanical study on shoes or physical aids.
- (3) biophysical control of growth, repair and remodeling of musculoskeletal systems using mechanical stress and electromagnetic fields.
- (4) prevention of disuse change of bone and joints, and respiratory function.
- (5) development of rehabilitation program for severely deconditioned (cancer and other progressive diseases).
- (6) Study on disability stages for various neuromuscular diseases.

References

(See Department of Rehabilitation Medicine)

Division of Diagnostic Pathology

Professor (Director)

Masashi Fukayama, M.D., Ph.D. *

Lecturer

Hisako Endo, M.D., Ph.D. (Deputy Director)

Noriyoshi Fukushima, M.D., Ph.D. *,

Hiroshi Uozaki, M.D., Ph.D. *

Lecturer (Hospital)

Kenji Kashima, M.D., Ph.D.,

Yutaka Takazawa, M.D., Ph.D.

Toru Motoi, M.D., Ph.D. (visiting researcher, USA)

Associate

Junji Shibahara, M.D., Ph.D.,

Tetsuo Ushiku, M.D., Ph.D.

Satoshi Ota, M.D. *, Ph.D.,

Tateru Ishida, M.D., Ph.D. *

Akiteru Goto, M.D., Ph.D. *

Clinical Fellow

Moon-Sung Chang, M.D.

Homepage <http://pathol.umin.ac.jp/>

Introduction and Organization

Department of Human Pathology and Diagnostic Pathology (*) and Division of Diagnostic Pathology of University Hospital have been merged to function as a unit, like other departments of clinical medicine. This union declares the responsibility of our department for the pathological practice (autopsy and surgical pathology) of the University Hospital, and education and research of human pathology. It is also expected to facilitate the translational research in the hospital.

The proper staffs in 2005 were 1 lecturer, two lecturers (hospital), two associates, and a clinical staff. Lecturer Dr. H Endo was the Deputy Director of the Division in 2004-5.

We celebrated the 30th memorial year of the Division of Diagnostic Pathology, and published a commemorative issue in 2005.

Clinical activities

Annual statistics of the pathology practice in 2004 are 12,534 cases of biopsy, 603 frozen histology, 17,845 cytology and 109 autopsy (21% as autopsy rate). In 2005, these are 12,672 biopsy, 693 frozen, 18,515 cytology and 114 autopsy cases (21% as autopsy rate).

Clinico-pathological conferences (CPCs) for the autopsy cases are held every month in the hospital, and two autopsy cases are discussed in each conference. 105th – 114th CPC were held in 2004 and 115th – 125th in 2005. CPCs of surgical pathology are regularly held for tumors of thorax, upper gastrointestinal tract, neurosurgery, liver, pancreato-biliary tract, urology, gynecology, mammary gland, and orthopedics, and for biopsy of liver, kidney and skin.

Our aim for surgical pathology is to provide the correct diagnosis as soon as possible. We are addressing two challenging issues. The one is the 'one-day pathology' using the specific histoprocessing machinery. We

have adopted a continuous rapid tissue processing system (CRTP), which have been developed by Prof. Morales at Department of Pathology, Minami University. In order to shorten the turn around time (TAT) in the University Hospital, the diagnostic system of staff pathologists and residents is being altered. Chief technician, Mr. Kaneko is taking a central role in further improvement of CRTP. The other issue is to apply molecular medicine to the diagnostic practice. We have developed the diagnostic system for the gene rearrangement analysis of lymphomas and for the chimera gene analysis of soft tissue sarcomas.

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 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 five interns in 2005 for the second year program of their internship.

Research activities

We are now 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 the candidate gene products are generated. In addition, to facilitate the screening process of immunohistochemistry, we are now in the process of constructing the tissue array of neoplastic and non-neoplastic tissues.

References

See the corresponding section of Department of Human Pathology and Diagnostic Pathology

Department of Corneal Transplantation

Associate Professor

Shiro Amano, M.D., Ph.D.

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

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.

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University hospital Medical Information Network (UMIN) Center

Professor

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

Associate Professor

Noriaki Aoki, M.D., Ph.D, M.S.

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

Introduction and Organization

The University hospital Medical Information Network (an original name was the University Medical Information Network: UMIN), was established in 1989. While general-use computer systems had been implemented at all national university hospitals around the end of the Showa era (late 1980s), Dr. Kaihara, a chair and professor of Hospital Computer Center, the 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 accepted a budget to initiate the UMIN Center. The UMIN Center was founded within the Hospital Computer Center, the University of Tokyo Hospital, and officially started in March, 1989. Followings were purposes of the UMIN center, which were initially described in 1989 (No.6 was added later)

1. provide up-to-date information for health care professionals
2. promote digitalized communication among health care professionals
3. support collaborative project 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 N1 protocol, which was developed in Japan and was the only solution at the time to connect together general-use computers of the five major computer vendors in Japan, although it was poor in function, supporting only line-mode, character-based terminals. Dr. Tsunetaro Sakurai became an associate professor as the first UMIN exclusive staff.

In 1994, we started service through the Internet whose spread began as in those days. A number of UMIN users had been gradually increased mainly on an E-mail service.

In 1996, Dr. Takahiro Kiuchi took up his new post while Dr. Sakurai promoted to a professor at the Hokkaido University, and updated the system to web-based. With a rapid spread of the Internet in Japan, UMIN users had been drastically increased afterwards.

The UMIN Center, then started to provide three major information services, (1) ELBIS (Electronic Library for Biomedical Sciences) since 1997, (2) INDICE (Internet Data and Information Center of Clinical Research) since 2000, and (3) EPOC (Evaluation system of Postgraduate Clinical training) since 2004.

In April, 2002, the UMIN Center became independent entity as the University hospital Medical Information Network Center (UMIN) by an internal arrange-

ment at the University of Tokyo Hospital. In 2003, a budget for new professor position was officially approved by the Ministry of Education, Culture, Sports, Science and Technology. Then, Dr. Kiuchi was promoted to the first professor of the UMIN Center on April 1, 2004. On October 1, 2004, Ms. Hisako Matsuba arrived at the post of the associate whom the lower part diverted the associate professor post. She resigned from her job in the end of March, 2006, and, Dr. Noriaki Aoki, an assistant professor of the School of Health Information Sciences, University of Texas Health Science Center at Houston, became an associate professor of the Center.

In addition to the professor and associate professor, the center employs one part-time staff assistant, six contract computer operators, and four to five system engineers, who are responsible for computer administration, operation maintenance support, and software development.

Teaching activities

We provide one lecture for medical school students, Medical Literature Informatics by Dr. Kiuchi, and two lectures for MPH students: Science Communication by Dr. Kiuchi and Health Communication by Dr. Aoki.

In addition, 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. These sessions and symposiums were broadcasted through the MINCS system, and can be downloaded as VOD from the UMIN server.

Research activities

The two main distinguished characteristics of researches at the UMIN Center, which are different from studies at other medical informatics programs, are followings.

(1) Researches for health informatics and communication

The UMIN Center is the only one research institute that study health informatics and communica-

tion-related researches, such as the Internet, satellite communications.

(2) Research targeting on health information science, not healthcare information practice

Currently, main topics of researches at most medical informatics programs in Japan focus on study for information for healthcare practice, such as hospital information system, electronic medical record system, telemedicine, and electronic billing system. In contrast, the UMIN Center has focused on the information systems for medical science, such as medical literature database, data registry for clinical studies, information system for medical education.

The followings are current research topics at the UMIN center.

(1) UMIN activities related Research

Most systems developed at the UMIN Center have been subjects for the research. We especially reported and published systems utilizing advanced technologies and having scientifically meaningful concepts at the academic conferences.

(2) Information system for clinical epidemiologic studies

We have developed and applied information systems for clinical epidemiological studies. Recently, we have focused on research for electronic format and standardization that are related to clinical research, such as CDISC. We utilized the achievements for medical research data center at the UMIN.

(3) Study about security of an information network Virtual Private Network (VPN), secure transaction with electronic mail (encryption), which have been also utilized for system management for UMIN center.

(4) Study plan development / a statistical analysis of clinical studies

In cooperation with clinicians, the UMIN Center performs development of 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 sys-

tems to utilize the results in clinical practice.

- (5) Technology assessment of health information and communication technologies

Although information technology is expected to play an important role in health care, its comprehensive usefulness, including cost-effectiveness, has been rarely evaluated. We conducted literature review in 2003 and concluded that there were few cost-effectiveness analyses for telemedicine program even though many telemedicine programs have been installed throughout many developed countries, such as the USA and Japan. Based on the review, we have done cost-effectiveness analysis for information technologies.

- (6) Research for health communication

Recently, "health communication" is becoming important concept in order to distribute the clinical results for population-based clinical outcomes improvement. We have conducted health communication research, which is focused on knowledge and skills in "informatics" and "communication".

- (7) Research for edutainment

To disseminate clinical knowledge and information to lay persons, it is important to consider about "easy-to-understand" and "acceptable by un-knowledgeable persons". We focus on studies related to media, entertainment, and interface design. For example, we have conducted development and evaluation of edutainment tools for health education to type-1 diabetes patients as concrete application.

- (8) The 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 been hardly utilized for quality improvement, patient safety or medical management. We have deployed an interactive web-based patient registry system with real-time feedback system of quality indicators (QIs).

- (9) Research regarding medical management

It is important to make proper judge and decision to achieve the optimal outcomes, which is called as management. However, scientific researches and evaluations related to patient safety, quality improvement and medical management have not

been?are not 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 for medical error prevention and quality improvement.

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Organ Transplantation Service

Director Professor

Masatoshi Makuuchi

Homepage

Organ Transplant Service started to function since 2003. In the Western countries the solid organ transplantation is widely performed and in contrast deceased donor organs are extremely rare due to religious and cultural traditions. In Japan the number of the recipients from the deceased donors has been limited around 40 under the act of law. The University of Tokyo Hospital has aggressively performed organ transplantation. In 1966, kidney transplantation for chronic renal failure was firstly performed in Japan. In 1996 the living donor liver transplantation was performed and totally 352 patients underwent liver transplantation. 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.

Department of Cell Therapy and Transplantation Medicine

Associate Professor

Shigeru Chiba, M.D., Ph.D. (Hematology-Oncology)

Lecturer

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

Associate

Noriko Hosoya, M.D., Ph.D. (Hematology-Oncology)

Homepage <http://www.h.u-tokyo.ac.jp/mukin/index.htm>

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 three 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.

Several clinical studies with allogeneic stem cell transplantation have been also conducted. These include RIST for pancreatic cancer, transplantation from a donor with mismatched HLA at two loci or more. All these studies are approved by the 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.

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 and leukemogenesis. 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 two years are listed in the references.

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Department of Endoscopy and Endoscopic Surgery

Associate Professor

Takao Kawabe, Ph.D.

Homepage

Introduction and Organization

Department of Endoscopy and Endoscopic Surgery was 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.

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, polypectomy for colonic polyps, endoscopic biliary

stone removal, and endoscopic stenting for biliary malignant diseases, 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, radiologic 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 for medical students 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 Department of Endoscopy and Endoscopic Surgery

	1997	1998	1999	2000	2001	2002	2003	2004	2005
UGI* endoscopy	4384	5555	5667	5923	6346	7324	7920	7597	8265
Colonoscopy	1398	2415	2472	2799	3212	3529	3873	3728	4084
Bronchoscopy	190	239	282	233	194	220	207	194	212
EUS**	347	562	569	470	479	583	586	476	461
Laparoscopy	19	7	2	0	-	-	-	-	-
Otophino-laryngological examination	131	96	99	115	154	93	68	61	89
Gynecological examination	272	213	153	149	181	103	124	139	88
Total	6741	9087	9244	9689	10566	11852	12778	12195	13199

*UGI; upper gastrointestinal, **Endoscopic ultrasonography

Research activities

Our researches cover a variety of fields including the upper and lower gastrointestinal tract and the pancreaticobiliary system. They are mainly performed in cooperation with the department of Gastroenterology.

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Clinical Research Center

Professor

Masao Omata, M.D., Ph.D.

Associate Professor

Yoshihiro Arakawa, Ph.D.

Associate

Fumihiko Kanai, M.D., Ph.D. (Transferred to Clinical Drug Evaluation Endowed Department on Nov. 2005)

Hirotsugu Watabe, M.D., Ph.D. (Appointed on Dec. 2005)

Homepage <http://www.h.u-tokyo.ac.jp/gcp/home/index.htm>

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, 2006, is comprised of one professor, one associate professor, one associate, five pharmacists, seven nurses, one clinical psychologist and three officials, of which one pharmacist and five 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: a division of consultation on protocol development (one associate professor and one associate), a division of pharmaceutical administration (three pharmacists), a division of clinical research coordination (seven nurses, two pharmacists and one clinical psychologist) and a 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 43 new protocols and 55 ongoing protocols for industry-initiated clinical trials in fiscal 2004. We also dealt with 3 new protocols for investigator-initiated regulatory clinical trials and 34 investigator-initiated non-regulatory clinical trials, which include the ethical use of non-approved drugs. A peer-review meeting 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, pre-registered review members from our hospital (pharmacists, doctors, nurses) and the staffs of the center. We also dealt applications for changes in the initial application documents (347 applications), safety information (396 reports), and other reports in fiscal 2004.

As for pharmaceutical administration, we took charge of 102 clinical trial drugs and filled 812 prescriptions in fiscal 2004. 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 pro-

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) supported the implementation of all the ongoing regulatory clinical trials in fiscal 2004. 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 2959 times of coordination of outpatients' visits and medical treatments of inpatients in fiscal 2004. CRC also supported the implementation of four investigator-initiated non-regulatory clinical trials partly. In 2005, we introduced a principle that beneficiaries should pay for part of a personnel cost of CRCs and adopted two 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 consultation division started at 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 to 4 times a year and a symposium every year. The division dealt with 34 investigator-initiated clinical trials which include the ethical use of non-approved drugs in fiscal 2004.

Teaching activities

The Center is taking charge of a part of bedside learning (BSL) of medical students in collaboration with the Pharmaceutical Department. The Center also accepted 90 third grade students of the Faculty of Pharmaceutical Sciences for visit and 36 fourth grade students in five groups for training. 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 fourth grade student and two graduate students belonged to our research labs in fiscal 2004.

The Center is involved as an on-the-job training institution in CRC training programs. In fiscal 2004, we accepted 8 three-week trainees from the program operated by Pharmacist Training Center.

Research activities

We performed the publication of 22 original papers written in English, 2 original papers in Japanese and 7 review papers in Japanese and the 45 presentations in academic conferences in 2004-2005.

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Division of Tissue Engineering

Director & Professor

Tsuyoshi Takato, M.D., Ph.D.

Visiting Associate Professors

Ung-il Chung, Ph.D. (Vice Director),

Keiichi Hishikawa, Ph.D.,

Kazuto Hoshi, Ph.D.,

Hiroyuki Koyama, Ph.D.,

Seishi Ogawa, Ph.D.,

Satoru Yamagami, Ph.D.

Visiting Research Associates

Toshiyuki Ikeda, Ph.D.,

Takeshi Marumo, Ph.D.,

Toru Ogasawara, Ph.D.,

Naoshi Ogata, M.D.,

Makoto Ohba, Ph.D.,

Takahiro Suzuki, Ph.D.,

Seiichi Yokoo, Ph.D.,

Homepage: <http://square.umin.ac.jp/t-e/>

Introduction and Organization

Division of Tissue Engineering was established as a special medical office in The University of Tokyo Hospital, in October 2001 and has a fully equipped 800 m² laboratory on the 8th floor of the Inpatient Ward B. Division of Tissue Engineering consists of Department of Bone & Cartilage Regenerative Medicine (Takeda Chemical Industries, Ltd.), Department of Vascular Regeneration (Daiichi Pharmaceutical Co), Department of Regeneration Medicine for Hematopoiesis (Kirin Brewery Co., Ltd.), Department of Corneal Tissue Regeneration (ArBlast Co., Ltd.), Department of Clinical Renal Regeneration (Mochida Pharmaceutical Co., LTD.), Department of “Fujisoft ABC” Cartilage & Bone Regeneration (FIJISOFT ABC INCORPORATED.). We have invited talented personnel of various fields from home and abroad. One visiting associate professor and one or two visiting research associates who are assigned to each department are conducting research with many post graduate students. Aiming at clinical application within a few years, the researchers continue their studies to make the center function as a translational research center.

Tie-up with companies, technical transfer, patenting developed technologies, producing materials for treatment at a GMP level, safety evaluation studies and organization for clinical trials are necessary in order to realize regenerative medicine, which is now recognized as a national project. As foundation and operation of venture companies as well as industry-university– government cooperation is essential to the success, it seems that state-level efforts are necessary. It is expected that broad progress in tissue engineering technologies and regenerative medicine contributes to treatment and drug discovery of all medical fields regardless of specialties.

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

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

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

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

September, 2002 Department of Regeneration medicine for Hematopoiesis founded by a donation from KIRIN Brewery Co., Ltd.

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

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

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

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

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

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

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

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

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 and 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 Fuji Software, 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.

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 Department of Regenerative Medicine for 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, clinical study on bone implants into non-loading parts (IRB approval number #1310) will be started by the end of March. 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. (Actually,) Department of Plastic Surgery is conducting research using this facility.

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Hospital Planning and Management

Associate Professor

Tomoaki Imamura, M.D.

Associate

Hideo Yasunaga, M.D., Hiroo Ide, M.A.

Homepage <http://www.cc.h.u-tokyo.ac.jp/mulins/kikakushitsu/index.htm>

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 instructors from the Department of Planning, Information and Management, and boasts a team of two pharmacists, two nurses, one engineering

staff member, and ten 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 and strategy

Based on the hospital management analyses, the division designs short-term management planning and strategy proposals, 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 wing
- Enhanced functions in the inpatient ward (expansion of ICU/CCU, increase in number of beds in the Psychiatry Department)
- Reduced the average length of hospital stays, and improved the bed occupancy rate

- Achieved reductions in medication 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 to set up 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.

The division submitted an application for “The University of Tokyo Hospital Special Zone” to the government’s “Special Zones for Structural Reform” under the theme of deregulating the Pharmaceutical Affairs Law. In Japan, there are certain medicines which cannot be used due to delays in their approval, despite their having been approved overseas. There are also certain highly-advanced technologies which have had their approval for insurance coverage delayed despite their medical effectiveness having been demonstrated. The concept behind the university hospital’s application is to allow these medicines and technologies to be used at the University of Tokyo Hospital. The University of Tokyo Hospital posed to society at large that the inconsistencies in the Japanese medical system should be eliminated. Our concept had a significant impact on the ensuing reforms to that medical system.

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 one doctoral student from the Department of Medical Informatics and Economics at the Graduate

School of Medicine, and one master’s student and one research student from the Department of Clinical Bio-informatics Research Unit at 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 healthcare policy and healthcare economics.

(1) Research in healthcare management

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.

(2) Research in healthcare policy

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.

The division is also undertaking comparative studies between medical systems in Japan and other developed countries, as well as empirical studies

related to the disparity of domestic and imported prices of medical equipment, and studies into the career paths of medical doctors.

(3) Research in healthcare economics

Using the contingent valuation method, the division is carrying out research related to the benefit evaluation of healthcare services. The division is also running empirical studies on the distributive efficiency of healthcare services, using cost analyses and cost-benefit analyses.

In addition, the division is also conducting economic analyses related to the effects that the promotion of preventative medicine has had on controlling national medical expenses.

Furthermore, the division is also conducting economic analyses on medical safety (research on cost analysis of medical accidents, and analysis on the cost effectiveness of medical safety measures).

(4) Health-related risk analysis and research

Risk analysis is comprised of risk assessment, risk management, and risk communication, and is a new approach for minimizing all kinds of damage. Based on this technique, the division is investigating and analyzing what exactly is necessary to minimize damage caused by incidents involving health risks. In recent years, there has been a rising necessity for the protection of citizens from the threat of terrorism. We have been conducting research to develop effective measures, especially against foodborne bioterrorism and chemical terrorism. Furthermore, in light of the globalization of recent years, a key issue has been food safety standards—the bringing into synch of the standards of individual countries, and the development of unified international standards. International standards are deliberated and determined at the Codex Alimentarius Commission (CAC). We use the risk analysis approach to study the various issues related to food safety which are discussed at the CAC.

In terms of risk communication, we conduct research on the disparities between the public information released by government agencies and the information circulated by the media. We also conduct research on risk communication for managing crises during times of health hazards. Furthermore, for the purpose of empirically clarifying whether

risk communication can actually reduce damage, we are investigating and studying the effect that displaying allergy-causing substances on food packaging has on reducing incidences of food allergies.

(5) Research into health statistics

The division conducts a great deal of health-care-related statistical research and analysis. One of these is a cohort study on Kanemi rice oil poisoning. Recently, thanks to improvements in verification technology, it has become possible to measure the concentration of dioxins in the blood. We are conducting investigations and research on the relationship between the concentration of dioxins in the blood of patients with Kanemi rice oil poisoning and their clinical symptoms.

We are also conducting resident surveys to ascertain the actual facts on allergy diseases and symptoms, as well as follow-up surveys to investigate the allergy-causing substances.

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Department of Child Psychiatry

Professor

Nobumasa Kato, M.D., Ph.D.

Specially Appointed Associate Professor

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

Specially Appointed Lecturer

Keiichiro Watanabe, M.D., Ph.D.

Specially Appointed Associate

Soo-Yung Kim, M.D., Ph.D.

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

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

Staff and faculty in the Department of Child Psychiatry consist of 7 psychiatrists including 3 full-time child psychiatrists and 10 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). In the year of 2005, services were offered to more than 300 new patients. Among these new patients, PDD was the most prevalent diagnosis (nearly 40%), followed by tic disorders and AD/HD. 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. Among follow-up patients, PDD was also the most prevalent diagnosis (approximately 50%), followed by tic disorders, stress-related disorders, MR and AD/HD. Approximately 40% of the patients at follow-up clinic were adult patients, highlighting the need for long-term follow-up in patients with developmental dis-

abilities.

Clinical activities are largely divided into two areas of general child psychiatry outpatient services and interventions for developmentally disabled children. Services for the general child psychiatry outpatients are provided by psychiatrists in the areas of pharmacotherapy, psychotherapy, psychoeducation and they 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.

Teaching activities

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 lectures and is offered twice a year, with a total of approximately 100 trainees per year. Course B is offered for a duration of 6 months with ten or more trainees per year including graduate students of the Department of Education. Also, one seminar and one symposium is held each year in order to facilitate understanding of mental development and developmental disorders among the general public.

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 activities

We participate in investigation of etiology and development of effective treatment on PDD and AD/HD, which are organized 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 are 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 effectiveness of the present interventions for children with PDD are conducted.

A comparison study of the effectiveness of individual treatment and "short-term group therapy" in a randomized control study is being undertaken.

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 en-

vironment 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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Clinical Genomics

Professor

Shoji Tsuji, 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, an endocrinologist, and neurologists), an urologist, a dermatologist, a staff of the department of clinical laboratory medicine and faculty members of the Departments of Human Genetics and Nursing Science.

ogy. We are also collaborating with Clinical Laboratory Center, Pharmaceutical Services, Departments of Planning Information and Management, Gastroenterology, Cardiovascular Medicine and Neurology have started clinical pharmacogenetics service since August 2006.

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 4th Friday 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 Ophthalmol-

Cooperative Unit of Medicine and Engineering Research

Professor

Shinichi Takamoto, M.D., Ph.D.

Homepage <http://plaza.umin.ac.jp/~ikourenk/>

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 Bioinformatics, Clinical Vascular Regeneration, Bone & Cartilage Regenerative Medicine, Cartilage of Bone Regeneration, Department of Immunotherapeutics (Medinet)

Engineering and Pharmaceutical Research

Chemical System Engineering, Mechanical 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 Biomedical Materials and Systems, Center for Disease Biology and Integrative Medicine Clinical Biotechnology, Research Center for Advanced Science and Technology, Institute of Industrial Science

Introduction and Organization

The application of an advanced bioscience to a new technical development of clinical medicine has become an important subject for research in the 21st century. We 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.

Research activities

Development of Advanced Stereotactic Radiation Cancer Therapy System

Department of Radiation Oncology

Nuclear Engineering Research Laboratory

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 _m 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.

Department of Clinical Bioinformatics

Department of Clinical Bioinformatics

Chemical System Engineering

Our specific targets include clinical support information systems (e.g.: electronic medical records and nursing support information systems) to support clinical practice with knowledge gained from genomic information; clinical testing information systems to support genome-based drug development and translational research; database systems to integrate disease and genomic information; and information management systems of genome and clinical information.

Surgical Robot System Lab.

Robotics, Dynamics, and Control Laboratory

Department of Mechano-Informatics

University of Tokyo

To develop: robot systems for endoscopic cardiac surgery, small-occupancy endoscopic robots, virtual stillness technology for cardiac surgery, and highly reliable surgical robot systems

Vascular Biomechanical Engineering Laboratory

Department of Vascular Surgery

Department of Tissue Engineering, The University of Tokyo Hospital

Medical Precision Engineering Laboratory, Institute of Environmental Studies, 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. To develop osteosynthetic devices.

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 Medi-

cine

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

Division of Biomedical Materials and Systems, 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 physiology, Computational mechanics

Department of Cardiothoracic Surgery, The University of Tokyo Hospital

Biomechanics Laboratory, Graduate School of Frontier Sciences, The University of Tokyo

Inhibition of aseptic loosening of artificial joints by nano-grafting of a Objectives and Research Fields. Development of multi-scale, multi-physics heart simulator and its clinical application. Molecular and cellular physiology, Computational mechanics.

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

Department of Pharmacy

Professor

Hiroshi Suzuki, Ph.D.

Associate Professor

Kousei Ito, Ph.D.

Assistant Professor

Akihiro Hisaka, Ph.D.

Associate

Yoshitsugu Yanagihara, Ph.D.,
Kazuo Takayama,
Masashi Honma,

Tomonobu Uchino, Ph.D.,
Erika Sugiyama,
Nobuhiro Yasuno Ph.D.

Tappei Takada, Ph.D.,
Takehito Yamamoto,

Homepage <http://square.umin.ac.jp/todaiyak/index.htm>

Introduction and Organization

We have eleven faculty members, 47 pharmacy staffs, 32 pharmacy residents, and 5 graduate students and 4 undergraduate students from the faculty of pharmaceutical sciences (fiscal year 2005).

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, bar code label printer, and automatic dispensing system 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). They also do mixing of injections at each staff station of ICU, CCU, HCU (both the surgical department and internal department), internal medicines for hematology and oncology. 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. 2,150 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.

- ① Investigation of carrying medicines and the side effect histories, allergy histories etc. at the time of hospitalization
- ② Procurement and appraisal of patient's basic information about the disease, compilation of the medicine history
- ③ Participation for conferences
- ④ Arrangement and mixing of injections for each patient
- ⑤ Monitoring of medication guidance and the side effect for the patient, and compilation of guidance record
- ⑥ Offering the doctor with drug information, prescription design support and detailed contents of medication guidance to each patient
- ⑦ Investigation and management of ward stock medicine. We extended these activities to 12 floors and 17 diagnosis and treatment courses

Statistical Data (fiscal year 2005)

Number of items on in-hospital formulary:

approx. 2,150

Number of prescriptions filled (annual)

out-patients: 483,818

(outside:	418,549)
(inside:	30,910)
(chemotherapy:	4,359)
in-patients:	407,878
(oral and external:	181,739)
(injection drugs:	201,851)
(IVH:	19,360)
(chemotherapy:	4,928)

TDM consultations (annual): 17,941

Numbers of hospital pharmaceutical cares (annual): 5,786

Educational Activities

We have lectures for the students in the health science and nursing of the medical department (Clinical Pharmacokinetics part in the Pharmacology and Toxicology (compulsory subject)) and for the students in the medical course of the medical department (Pathogenic and Pathology (an optional course)). In those lectures, we give outlines of drug absorption, distribution, metabolism and excretion. We also introduce the theory of pharmacokinetics and pharmacodynamics to understand clinical drug-drug interactions. We take care of 2 to 3 medical students (M1 and M2) for 2 weeks as free quarter students and teach them basic molecular and biochemical techniques, as well as the pharmacokinetic theory. We also take care of all medical students (M3 and M4) for 3 days each and teach them clinical pharmacetics, which is conducted as a part of clinical practice of the course (compulsory subject). During this course, students are expected to acquire knowledge for proper prescription design and medication. Moreover, it also helps understanding of the role of pharmacists in a clinical team and importance of the cooperation.

We also hold two series of lectures for the undergraduate students in the faculty of pharmaceutical sciences: Clinical Pharmacy I (compulsory subject) and Clinical Pharmacy II (an optional course). They are educated for the clinical pharmacology and pharmacokinetics. At the graduate school of pharmaceutical sciences, we are in charge of "Advanced Theory for Medical Pharmacy" as a cooperator of clinical pharmacokinetic lectures (every other year), where recent developments of the working field as well as the direction and future vision of pharmacists are reviewed. We are training 150 students (a year) from the faculty of

pharmaceutical sciences from our university and outside. Moreover, we have one-year training course for post-graduates (32 pharmacists in 2005). In addition, technical workshops are held every month to promote life-long education of pharmacists who are engaged in regional medical care.

Research activities

A proper medication requires scientific evidences. However, it is not fully understood that what is the target for main and side-effect of the drug, 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) Intracellular trafficking and dynamic rearrangement of transporter complexes.
- 3) Polymorphism of drug metabolizing enzymes and transporters. Quantitative prediction of clinical effects.
- 4) 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
Integrative Medicine**

Division of Basic Medical Sciences (2)

Professor

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

Lecturer

Noriko Takahashi, M.D., Ph.D.

Assistant Professors

Masanori Matsuzaki, Ph.D., un Nogichi, Ph.D., akuya Kishimoto, Ph.D.

Homepage <http://www.bm2.m.u-tokyo.ac.jp/>

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 in January, 2006. Our division belongs to the Section of Functional Biology field in the Graduate School of Medicine, and our division is named the Division of Biophysics in the graduate school.

Teaching activities

In 2005, we were involved education in the graduate school. We have two graduate students in our own graduate school, and two from the Graduate School of Advanced Studies and one from the Graduate School of Science in the University of Tokyo.

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) Dynamics of synapses in the cerebral cortex.

We have developed a method to stimulate and control single synapses in the cerebral cortex with the use of two-photon excitation of photoactive glutamate analogs. Our investigations have revealed that the major functions of synapses depend on their structure. We have thus shown that small synapses are ready to learn, enlarging rapidly (within 10s) after stimulation, whereas large synapses are structurally stable and act as long-term memory traces. These observations suggest that learning, memory, and other activities of the brain are mediated by changes in synaptic structure, and that they can be directly visualized. Moreover, we are now in a position to manipulate synaptic plasticity with a laser beam at the level of the individual synapse. Such notions and methodology will be further exploited to understand brain functions and disorders.

- 2) Exocytosis. Exocytosis is the most essential function of synaptic terminals and secretory cells. Knowledge of the mechanisms of and the ability to control exocytosis artificially have been limited, however. With the use of two-photon excitation-based simultaneous multicolor imaging of various tracers, we have, for the first time, visualized exocytosis in intact islets of Langerhans, pancreatic acini, the adrenal medulla, and synaptic preparations. By further extending our approaches, we aim to develop new methods for imaging and control of secretory functions and their molecular processes in the cerebral cortex and secretory tissues.

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Division of Biomedical Materials and Systems

Professor

Takashi Ushida, Ph.D.

Associate Professor

Yasuyuki Sakai, Ph.D.

Associate

Kouhei Tsuchiya, M.D., Ph.D.

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

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 an introductory lecture concerning medical application of chemical engineering at the Komaba Campus, a special lecture concerning organs and biosystem engineering at the Chemical System Engineering 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

The general objective of Prof. Sakai's laboratory is to organize experimentally human systems or its subsystems such as organ or tissue using cultured human cells for fundamental understanding of systemic responses of a human body or organs and biomedical or environmental applications. At present, we need several different technologies to achieve the goal in addition to usual cell culture technologies. These include in vitro control of the growth and differentiation of organ stem or progenitor cell populations, cultivation technologies ranging from micro- to clinically significant-sizes, three-dimensional microfabrication of biodegradable organ templates, etc. About such topics, we are actively doing collaborative research with other institutes outside Univ. of Tokyo. The most important thing is to organize these technologies originally derived from different academic background from engineering point of view.

- 3) Engineering of human large internal organs
- Design of inner microstructure of reconstituted human organs
 - Three-dimensional microfabrication of biodegradable organ templates
 - In vitro control of growth and differentiation of organ progenitor cells.....
- 4) Development of in vitro models for human organs and their applications
- Development of biohybrid simulator for absorption and biotransformation
 - In vitro models for lung alveolar tissue and its application to toxicity evaluation of gaseous chemicals or environmental samples
 - Micro-organ model devices

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Division of Clinical Biotechnology

Professor

Kazunori Kataoka, Ph.D.

Associate Professor

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

Lecturer

Keiji Itaka, M.D., Ph.D.

Associate

Nobuhiro Nishiyama, Ph.D.,

Younsoo Bae, Ph.D.

Homepage: http://www.cdbim.m.u-tokyo.ac.jp/research/01_04.html
<http://www.bmw.t.u-tokyo.ac.jp/>

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), which started in 2004 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 associate professor, one associate and several project staff members belonging to the CNBI and NBEP.

Our division focuses on the realization of nanomedi-

cine. 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 diag-

nosis-treatment" and "targeting medical treatment" and nanotechnologies are developing so quickly with increasing complexity that scholars in both areas find it hard to understand each other. For this reason, it is becoming increasingly difficult for medical doctors to locate technological seeds meeting their medical needs and for engineers to find ways of applying their technological seeds to corresponding medical needs. This situation prevents the effective development of revolutionary medical diagnostical and therapeutic inventions. Division of Clinical Biotechnology intends to create an optimal milieu where undergraduate and graduate students from the medical and engineering fields can respect each other's background, ignores the boundary and study the fusion area in order to achieve the common goal of developing intelligent nanodevices for the futuristic medical system.

Research activities

Drug delivery to the targeted site is strongly desired to enhance the drug function and minimize the side effects. In this regard, drug delivery systems based on self-assemblies of block copolymers (i.e., polymeric micelles) recently draw much attention as one of the medical applications of the nanotechnology. Block copolymers spontaneously form polymeric micelles, which are characterized by the core-shell structure and the size of ~100 nm, in aqueous media. The core of the micelles behaves as a nanoreservoir for drugs, while the coronal shell providing the biocompatible surface. Polymeric micelles can incorporate a variety of drugs including hydrophobic drugs, metal complex drugs, and macromolecular drugs such as proteins and DNA, and release them in a sustained manner or in response to environmental changes such as pH. The site-specific drug delivery can be achieved by conjugation of the pilot molecules on the surface of polymeric micelles. Thus, polymeric micelles behave as intelligent chemical nanomachines for the drug targeting.

The long-circulation of drug carriers is a requisite for the successful drug targeting. The main obstacles to long-circulation are considered to be glomerular excretion in the kidney and recognition by the reticuloendothelial system (RES) located at the liver, spleen and lung. Polymeric micelles can escape from those barriers in the body, resulting in stable blood circulation. An-

other 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 anti-tumor 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. Recently, we have developed the light-responsive gene carriers, and have achieved *in vivo* gene transfer in a light-specific manner. Further, polymeric micelles can be used for the tissue engineering without cell transplantation. Recently, polymeric micelles carrying pDNA encoding osteogenic factors were implanted to mouse calvaria bone defects in the form of calcium phosphate paste, resulting in rapid induction of bone regeneration. Thus, polymeric micelles are expected as useful nanocarriers of pDNA and siRNA for *in vivo* use.

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Division of Environmental Health Sciences

Professor

Chiharu Tohyama, Ph.D., Dr.Med.Sci.

Associate Professor

Seiichiroh Ohsako, Ph.D., D.V.M.

Assistant Professor

Masaki Takeyama, Ph.D.

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

Introduction and Organization

Division 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

Humans are exposed in our environment to various hazardous chemicals via food, air, and water. When these chemicals are absorbed, distributed and metabolized in the body, perturbation of homeostasis and adverse signs and symptoms of toxicity may occur. At the Division of Environmental Health Sciences, the adverse effects caused by exposure to an individual chemical or to mixtures of chemicals are identified, the dose response relationship for causing the adverse ef-

fects is determined, and the precise mechanism by which the toxicity is produced at the molecular and cellular level is elucidated by using two approaches.

The first approach is based on 'forward toxicology'. Here we start from a specific disease or health problem humans are facing in the real world that might be caused by exposure to certain chemicals in our environment and we determine if the adverse effects caused by exposure to the particular chemical or mixture of chemicals are similar to the adverse effects associated with the human disease or human health problem. This is done by exposing laboratory animals and cultured cells to increasing doses of the chemical or chemical mixture and identifying adverse effects, called 'end-points of toxicity', at each dose.

The other approach is 'reverse toxicology'. In this approach we utilize a particular laboratory animal model in which a specific adverse effect can be reproducibly observed, and we attempt to clarify the physiological significance of altered expression of genes and proteins in causing the adverse effect. In this 'reverse toxicology' approach we use modern, molecular biology based technologies such as global gene analysis and genetic engineering to identify the mechanism of toxicity at the molecular and cellular levels.

The primary goal of the Division's research program is to elucidate toxicity mechanisms for various envi-

ronmentally 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.

Division's Research Themes

1. Elucidation of mechanisms of toxicity at the molecular and cellular level for adverse effects of environmentally hazardous chemicals (dioxin, PCBs, and heavy metals).
2. Identification of differences in susceptibility to the toxicity caused by a particular environmentally hazardous chemical between different animal species and between different genetic strains of the same species.
3. Determination of the cause of such species and strain differences in sensitivity to an environmental toxicant at the molecular and cellular level.

Teaching activities

Unfortunately, ‘Environmental Toxicology’ is not fairly placed in the curriculum of medicine, pharmacy, nursing, and other allied health sciences at most universities. In addition to its research mission, the Division of Environmental Health Sciences has an equally important education mission. The Division is actively involved in educating graduate students and training postdoctoral fellows to become promising scientist leaders in the field of environmental health sciences in the future.

For the upcoming year, the Division will be responsible for a full credit course on ‘Principles and Applications of Environmental Health Sciences’. In addition, several lectures are to be given to graduate students for Master's degree as well as to undergraduate students at School of Medicine and School of Health Sciences and Nursing.

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Section of Animal Research, Division of Research Resources and Support

Professor

Akio Nomoto, Ph.D.

Associate Professor

Lecturer

Associate

Ken-Ichi Hanaki, D.V.M., Ph.D.,

Haruyuki Hirata, D.V.M., Ph.D.

Homepage [http:// www.cdbim.m.u-tokyo.ac.jp/research/01_06.html](http://www.cdbim.m.u-tokyo.ac.jp/research/01_06.html)

Introduction and Organization

Section of Animal Research (formerly Animal Center for Biomedical Research) was established in April 1971 to provide laboratory animal husbandry and veterinary consultation services for the investigators in the Faculty of Medicine. A full-time teaching staff, a veterinarian, was arrived in April 1972. The building was completed in March 1973, and the center began to provide services for animal experimentation in April 1973. The building has 7 floors and the basement.

Basement; operating room for plants, central heating plant room, electric-transformation room, animal quarantine rooms, etc.

1st Floor; office rooms, conference room, dressing room, etc.

2nd Floor; staff rooms, laboratories for this section staff, cage washing rooms, rabbit and rat rooms.

3rd Floor; SPF rodent rooms.

4th Floor; SPF rodent rooms and radioisotope laboratories.

5th Floor; procedure rooms (autopsy, surgery, x-ray) and

no-human primate rooms.

6th Floor; no-human primate, dog, pig rooms.

7th Floor; air-conditioning plant room.

Animal Center for Biomedical Research was at first a facility attached to the faculty. Today the animal center is one of sections, Division of Research Resources and Support, the Center for Disease Biology and Integrative Medicine (CDBIM).

The members of this section are 3 teaching staffs, 2 technical support staffs, head official 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. One of our missions is to provide quality care for all animals used in our building. The other is to assist the registered users in their mission of quality research with respect to the use of laboratory animals. In particular, research associates (attending veterinarians) have overall responsibility for the health and welfare of animals used in research. The office of this section is also the secretariat of the Ani-

mal 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 the principal investigator. The committee (Chair, Prof. Akio Nomoto) 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.

All investigators in the University of Tokyo are able to use facilities in our building after the registration. However the most of registered patrons are the investigators in the Graduate School of Medicine. The number of registered patrons was 729 in 2005.

Teaching activities

Our teaching responsibility is to give lectures on Laboratory Animal Science to the 2nd-year students of the Science Course III of the College of Arts and Sciences. The teaching staff of this section teaches 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

There is no regular teaching curriculum for graduate students. However Laboratory Animal Science is taught as a part of Microbiology.

Research activities

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

- (i) Detection of a trace amount of antigen in tissue.
The purpose of this research is the development of a signal amplification technique suitable for the detection of antigen in tissue. We have developed a new signal amplification technique using nucleic acid that would be suitable for the detection of immobilized antigen on protein chip or tissue.

Now we try to adapt the technique for the detection of PrP^{BSE} in brain. This study is collaboration with National Institute of Infectious Diseases (NIID).

- (ii) Elucidation of the mechanisms to escape host immunity by pathogen in parasitic infections.
We expect this investigation will be helpful for the development of new therapeutic approaches and drugs.

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Section of Radiation Biology

Professor

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

Associate Professor

Yoshio Hosoi, M.D.,Ph.D.

Lecturer

Takahiko Suzuki, Ph.D.

Associate

Yoshihisa Matsumoto, Ph.D.,

Atsushi Enomoto, Ph.D.

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

Introduction and Organization

The Section of Radiation Biology belongs to the Division of Research Resources and Support in Center for Disease Biology and Integrative Medicine. The main duty of the section is to support the use of radioisotope at Graduate School of Medicine. Historically, in 2003, the Department of Radiation Oncology and the Radiation Research Institute were joined to form a new department.

To maintain the facility of radiation research, responsible staffs at two facilities are elected from our department. Although the law that regulates the use of radioisotope in Japan was largely revised this year, the maintenance system and frequency of the use of radioisotope have not been changed.

Present staffs came from the previous departments. However, the position of the professor had been vacant since 2003. The present professor took the position on 16 June 2005. Since then, the new research projects have been carried out.

Although the supportive work is very important, education and research on effects of radiation on human bodies are the most important duties in this section. We cannot deny the fact that individual works have not

been integrated thus far, the present staffs are constructing a new group that plays a leading role in radiation biology.

Teaching activities

We are responsible for the education of basic radiation medicine for the 2nd 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, a new course for the 4th year medical students was opened this year. The 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 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, non homologous 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. In Rad51B mutant cells, the Rad51-dependent recombinational repair pathway is impaired. In addition, centrosome fragmentation 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. The growth of the mutant cells was reduced by the Chk1 and Chk2-dependent checkpoint activation at the S and G2 phases, leading to the reduction in Cdk1 and Cdk2 functions. Chromosome analysis revealed that the frequency of chromosome doubling was significantly increased in the mutant cells. Restoration of Cdk1 activity by ectopic expression reduced the frequency of chromosome doubling, suggesting that the checkpoint activation may cause chromosome doubling.

Thus, 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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Section of Bioinformatics

Associate

Kenji Hatano, M.D.

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

Organization

Section of Bioinformatics started in 2003 as a division of Research and Support of the Center for Disease Biology and Integrative Medicine. Targeting biomedical research support using information technologies, this division performs management and maintenance of the research network and information servers working with the Information Promoting Office of the Graduate School of Medicine.

Research activities

Medical terminology and ontology:

Standardization and systematization of medical vocabularies are major issue for appropriate utilization of medical information implied in various medical terms. We are committed the working group for the Japanese standard disease code master (standard vocabulary of Japanese disease names) and studying about the strategies for perform the standardization of Japanese medical vocabularies for electronic medical records. Using current techniques of systematization of terms and concepts, such as terminology or ontology, we are testing systematization of Japanese medical terms and concepts and automatic classification system for free medical words.

Distributed processing system for medical terms:

As an efficient method for the distribution of medical term information and promotion of the standard vocabularies, we focused distributed processing system using the network and are developing distributed methods service system in the internet for evaluation of utilities and effectiveness of the system.

Main targets of our research are:

- Standardization of medical vocabularies and coding system
- Biomedical terminology and ontology
- Distributed processing system for medical information using the internet
- Security of biomedical research network
- Privacy and anonymization of personal data in clinical research
- Digitalization and indexing of old Japanese medical libraries.

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Office of International Academic Affairs

Head

Kazuhiko Yamamoto

Assistant Professor

Joseph Green

Assistant Professor

Toshiyuki Maruyama

Foreign Member of the Teaching Staff

Christopher Holmes

Homepage

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.

Personnel

The office is headed by Professor Kazuhiko Yamamoto. Christopher Holmes joined as foreign member of the teaching staff in 1999.

Drs. Green and Maruyama share the duties of the Office of International Academic Affairs.

Activities

This document reports on the office's activities in these areas over the academic years 2004 and 2005 (April to March).

1. International Educational Exchange**1.1 Student counseling about education and research**

In 2004, there were 165 foreign students (28 countries) officially registered in the Graduate School of Medicine; in 2005, there were 162 from 29 countries. Many inquiries were received during this period from prospective applicants for foreign student and trainee status; responses were sent to 88 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.

Admission of foreign students to research positions or graduate study in Japan is extremely difficult, for a variety of reasons, but positions were found for 1 applicants of the 9 whose applications were channeled through the Office of International Academic Affairs in 2004 or 2005.

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 at the Sanjo Kaikan, a reception hall on the Hongo campus. It is attended by the Dean of the Faculty of Medicine, the teaching staff, and students: both in 2004 and 2005, about 80 people attended this event.

Another tradition since the mid-1970s is the Autumn foreign students' trip; In 2004, a group of 30 from 10 countries traveled to Tokyo DisneySea. In 2005, a group of 45 from 12 countries traveled to Lake Kawaguchi and Fuji-kyuko Highland.

Ryugakusei Ronbun Contest which began in 1999 was held in both 2004 and 2005. The authors presented their papers to interested fellow students and faculty and the better five 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, four University of Tokyo students have taken research electives at the University of Pennsylvania every year, and one student from the University of Pennsylvania have taken clinical electives at the University of Tokyo.

A new agreement on academic cooperation was signed between the Graduate School of Medicine of the University of Tokyo and the Ohio State University in May 2001. Since the start of the program in 2001, eleven University of Tokyo students visited to attend clinical electives at the Ohio State University.

Another new 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, eight University of Tokyo students visited to attend clinical electives at Johns Hopkins University.

Another new agreement on academic cooperation was signed between the Graduate School of Medicine of the University of Tokyo and Michigan Medical School in January 2005. Since the start of the program in 2005, two University of Tokyo students visited to attend clinical electives at Michigan Medical School.

Another new agreement on academic cooperation was signed between the Graduate School of Medicine of the University of Tokyo and the Munich University in February 2005. Since the start of the program in

2005, one University of Tokyo students visited to attend research electives at the Munich University, and one student from the Munich 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 two major research projects are underway, in nosocomial infections and in new and re-emerging infections. A total of 11 researchers were invited to Japan (571 researcher-days) and 18 Japanese researchers were sent abroad (84 researcher-days) in 2004, and a total of 11 researchers were invited to Japan (511 researcher-days) and 27 Japanese researchers were sent abroad (189 researcher-days) in 2005.

3. Education and research

3.1 Education

In 2004 and 2005, 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 2005, 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 2004 and 2005, 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.

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International Research Center for Medical Education (IRCME)

Director & Professor

Kimitaka Kaga, M.D.,Ph.D

Professor

Kiyoshi Kitamura, M.D.,Ph.D.

Associate Professor

Yuko Takeda, M.D.,Ph.D.

Lecturer

Hirotaka Onishi, M.D., Ph.D.

Guest Researcher

Takuya Adachi,M.D

Invited foreign professor

Ellen Cosgrove, M.D., FRCP

New Mexico University, School of Medicine

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

History and organization

Three years after it was first proposed, the University of Tokyo's International Research Center for Medical Education (IRCME) was established on April 1, 2000. The Ministry of Education, the University of Tokyo, and the Graduate School of Medicine established IRCME as a base for promoting international cooperative studies of medical education. We would like to express our thanks to all who have supported this center.

IRCME comprises a department of International Cooperative Study for Medical Education, Department of Planning and Coordination for International Cooperative Projects and Information on Medical Education, and a position for a visiting professor from abroad. We hope that the research in medical education carried out of IRCME will improve medical edu-

cation and health care in many countries.

One of IRCME's most important is to study and promote a broad view of medical education, and to make the results of our efforts available both within Japan and worldwide. We aim to promote international cooperation and to construct a database of educators, researchers, and clinicians interested and active in medical education. On behalf of the entire IRCME staff, we reaffirm our commitment to these goals.

Educational activity for medical education

In recent years, medical education has moved away from systems in which students merely observe their teachers interacting with patients; now students are increasingly expected to participate actively in their learning and in solving clinical problems. Moreover,

the knowledge required for modern medicine increased both in range and in depth. As educators and researchers, not only must we help today's students become familiar with problem solving

Contemporary biomedical sciences, advanced medical equipment, and computer-based sources of information, we must also ensure that appropriate attention is given to the ethical and socioeconomic aspects of medicine. With the goal of improving medical education, we do research on a broad range of topics including action research both at the University of Tokyo and at other universities. In doing so, it incorporates insights from medical anthropology and from experiences with international cooperation in many other fields into research aimed at maximizing the benefits of international cooperation in medical education. As contributions to the progress of medical education, the results of this research are made available both in and outside Japan via research papers, to her publications, presentations at academic meetings, and thorough new including the internet and a network of university hospitals linked by a communications satellite. Some activities of this department are listed below.

1. Research on theory and method in adult learning:

This includes analysis of published literature and other relevant materials, visits to and surveys of institutions with outstanding educational programs, and discussion with leaders in the field.

2. Action research to improve medical education:

- a. Development of curricula
- b. Improvement of educational methods (examples include faulty development, small group tutorials and problem-based learning, use of simulated patients to teach basic clinical skills, and a super-rotation system centered on primary care)
- c. Development of educational resources (collaborative research among multiple institutions to develop course work plans, materials for tutorials, audio-visual materials, simulated patients, models and simulators for teaching physical examination, and Objective Structured Clinical Examinations); evaluation of educational outcomes.

3. Research on the needs regarding international cooperation in medical education:

This includes analysis of published literature and other materials, collection of information from relevant organizations, site visits and surveys, and discussions with leaders in the field.

4. Action research on international cooperation in medical education:

This includes support for the development of curricula and other educational resources, and for the development of teacher-physicians.

Educational research activity

Emphasizing international educational cooperation in medicine, dentistry, pharmacy, nursing, nutrition, public health, and related areas, this department seeks to enhance the university's role in humanizing Japan's contribution to international development, by building a database of researchers and practitioners and by forming networks among individuals and institutions. Some activities of this department are listed below.

1. Coordinating the planning, establishment, and implementation of education and training for international cooperation in medical education projects initiated in Japan.
2. Forming and contributing to a world wide consortium of specialists working for international cooperation in medical education.
3. Holding a Forum on International Cooperation and Research on Medical education, and publicizing its proceedings.
4. Developing a database of information on Japanese researchers and practitioners interested and active in international educational cooperation in medicine.
5. Development of international cooperation projects in health professions education area budgeted by official development assistance (ODA), research grants, etc, especially in developing countries. Currently, several projects for Afghanistan are under implementation.
6. Support for international cooperation projects in health professions education area through the efforts on information gathering and interpersonal exchange in both domestic and international level. Currently, we have constructed strong relationship with the Committee for International Affairs (Japan Society for Medical Education), Na-

tional Institute for Public Health and International Medical Center of Japan in medical area, and St Luke's College of Nursing in nursing area.

International medical education activity

Medical education has recently shifted from methods focused on Inculcating biological knowledge to approaches that incorporate problem-based learning and integrated, fully humanistic viewpoints. As medical educators, we are responsible both for scientific and technical training and for rehumanizing our students. Furthermore, while we must teach medicine as it is now, the exponential increase in medical information requires us also to help our students develop the skills and approaches they need to become lifelong learners.

In these changing times, we realize the acute and pressing need to do interdisciplinary research on new methods in medical education and to make the results of our work widely available. International activities in medical education have important roles also within Japan: acquiring new information about approaches to medical education found in other countries and making that information available domestically can broaden the horizons of educators and improve the quality of medical education in Japan.

Since its founding on April 12, 2000, the International Research Center for Medical Education has worked both within in University of Tokyo and in a wider context, using the ideas outlined above as the basis for research intended to inform international cooperation in medical education and to develop tomorrow's medical practitioners. The Center is devoted to enhancing medical education and to a high standard of international cooperation.

Invited foreign guest activity Visiting Professorship

To facilitate international cooperative study and information exchange,

IRCME invites researchers from abroad who specialize in medical education.

Invited professors are chosen in part for their knowledge and experience in international coopera-

tion and medical education. They advise and instruction to IRCME on practical aspects of planning and promoting cooperative projects. They also collaborate on research projects with researchers in other parts of the University of Tokyo and in other academic organizations.

Activities

1. Giving practical advice and instruction on international cooperation in medical education.
2. Doing international cooperative research on international collaboration for medical education.
3. Doing research on interdisciplinary planning and coordination and on generalizing methods among various areas of specialization.

Visiting Professors

Thomas S Inui, ScM, MD: American Association of Medical College, Harvard Medical school

(June-September 2000)

Gordon L Noel, MD, FACP: Oregon Health Sciences University

(October 2001-March 2002)

Jerome R Hoffman, MA, MD: University of California, Los Angeles

(July-September 2002)

Daniel R. Wolpaw, MD, Case Western Reserve University

(Nov 2003-Jan 2004)

Georges Bordage, MD, PhD

University of Illinois Chicago (Feb-Jul, 2004)

Bounsai Thavisouk, MD

National University of Laos (Dec. 2004-Mar. 2005)

Edward Peskin, MD, FACP

University of Massachusetts Medical School

(Mar-Jun. 2005)

Helen Cosgrove, MD FACP: New Mexico University

(November 2005-April 2006)

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編 集 後 記

東京大学医学部年報は平成 4 年度から刊行されており、平成 7 年度からは日本語版（偶数年版）と英語版（奇数年版）が隔年で刊行されていました。平成 16 年度までは医学部年報編集委員会が編集を行っていましたが、17 年度から年報編集委員会が医学部広報委員会に統合されたのを契機に、今回お届けする 17 年度版からは日本語版と英語版をともに毎年刊行することによって、東京大学医学系研究科・医学部の教育・研究・診療等の活動をこれまで以上に広く公表する一助とすることになりました。

今回お届けするのは平成 17 年度版で、業績については暦年で 2004 と 2005 の 2 年分を掲載していただいてもよいという方針で編集しました。編集にあたっては、木内貴弘委員（年報編集担当）、山田喜朗医学部専門員をはじめ広報委員会の委員の方々、各教室の方々に大変ご努力いただきましたことをお礼申し上げます。

また、本年報は従来から東京医学の刊行物として東京医学会から刊行していただいておりますが、今回も引き続き東京医学会から支援していただいたおかげで、

医学部広報予算とあわせて日本語版と英語版とを同時に発行することができました。また今回から印刷データは Web データとしても作成して医学系研究科・医学部のホームページにも掲載されます。関係の方々のご尽力に感謝いたします。

なお編集には誤りのないよう関係者で努力したつもりですが、もし不備がありましたらご指摘の上、お許しいただきますようお願いいたします。

広報委員会委員長 大江 和彦

本年度は、収集した原稿をそのまま印刷できるように MS・WORD のテンプレートと執筆要綱を作成しました。ある程度の直しはやはり必要でしたが、まずまずのできだったと思います。次年度は、オンライン収集が実現できればと考えています。

広報委員会委員 木内 貴弘

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編集・発行者 東京都文京区本郷7-3-1 東京大学医学部内（〒113-0033）

財団法人 東 京 医 学 会

印 刷 者 ナカバヤシ株式会社 東京都板橋区東坂下2-5-1
